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Fluorous Parallel Synthesis of A Hydantoin/Thiohydantoin Library

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Abstract

Fluorous tagging strategy is applied to solution-phase parallel synthesis of a library containing hydantoin and thiohydantoin analogs. Two perfluoroalkyl (Rf)-tagged α -amino esters each react with 6 aromatic aldehydes under reductive amination conditions. Twelve amino esters then each react with 10 isocyanates and isothiocyanates in parallel. The resulting 120 ureas and thioureas undergo spontaneous cyclization to form the corresponding hydantoins and thiohydantoins. The intermediate and final product purifications are performed with solid-phase extraction (SPE) over FluoroFlash™ cartridges, no chromatography is required. Using standard instruments and straightforward SPE technique, one chemist accomplished the 120-member library synthesis in less than 5 working days, including starting material synthesis and product analysis.

Keywords

hydantoin; thiohydantoin; fluorous synthesis; parallel synthesis; solid phase extraction

1. Introduction

Solution-phase parallel synthesis has become an increasingly important method in medicinal chemistry. Many reaction and purification techniques and instruments, such as parallel reaction vessels, polymer-supported reagents and scavengers, solid phase extractions, and microwave reactions, have been employed in parallel synthesis. The conventional solution-phase parallel synthesis requires minimum method development effort. However, purification is an obstacle because chromatography is usually needed for each reaction mixture. On the other hand, polymer supported solution-phase synthesis simplifies the purification, but it has restrictions due to the heterogeneous reaction conditions which usually slow the reaction. Fluorous synthesis is a complementary type of liquid-phase synthesis that has the character of solution-phase reactivity and solid-phase type separation [1–4]. Fluorous synthesis employs perfluoroalkyl chains (Rf) as the phase-tag for easy separation. Since the light fluorous molecules have good solubility in common organic solvents, fluorous reactions can be conducted in a homogeneous environment with favorable reaction kinetics. The scope of fluorous reactions is similar to conventional solution-phase synthesis. The separation of reaction mixtures containing light fluorous molecules can be achieved by fluorous silica gel-based solid-phase extraction (SPE) or HPLC [5–7]. The capability of monitoring the reaction process and analysis of fluorous molecules by TLC, HPLC, MS and NMR is an additional advantage of fluorous synthesis. Since the early development by the Curran group in the late 1990's, light fluorous synthesis has quickly become an active research area. The fluorous tagging strategy has been introduced to make reagents [8–11], scavengers [12–16], protecting groups [17–21] and related tags [22–23] for parallel and mixture syntheses [24–28]. It has also been used in peptide and oligosaccharide syntheses [29–31].

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Hydantoin is an important heterocyclic core that exists in many natural products such as hydantocidin and aplysinopsins (Scheme 1). Hydantocidin is produced from *Streptomyces hygroscopicus*, which has potent herbicidal activity [32–34]. Aplysinopsins are isolated from marine organisms, and they exhibit cytotoxicity to cancer cells and ability to affect neurotransmitters [35–37]. Other hydantoin derivatives also exhibit a broad range of biological activities in medicinal (antitumor, anticonvulsant, antimuscarinic, antiulcer, and antiarrhythmic) [38–42] and agrochemical (herbicidal and fungicidal) [43–49] applications. In addition to solution phase synthesis [50–51], solid-phase synthesis of hydantoin has also been reported in the literature [52–56]. A common strategy in solid-phase synthesis is cyclization-assisted cleavage which combines the linker cleavage and ring formation in a single reaction step [57]. One of the first examples of cyclative cleavage of polymer support in solid-phase synthesis was developed in the preparation of hydantoins [58].

We recently reported a quick synthetic method for hydantoins and thiohydantoins by combination of fluororous tagging strategy with fluororous SPE technique [59–60]. Described in this paper is an application of this method in the parallel synthesis of a 120-member library of hydantoins and thiohydantoins.

2. Results and Discussion

Preparation of the 120-member hydantoin/thiohydantoin library was conducted following the synthetic route illustrated in Scheme 2. Fluororous amino esters **1** were subjected to reductive amination reactions with aldehydes. Intermediates **2** were then reacted with isocyanates or isothiocyanates to form corresponding ureas or thioureas **3** which then underwent spontaneous cyclization to displace the fluororous tags to yield the hydantoin or thiohydantoin rings. The product scaffold has three points of diversity. The scope for R¹, R² and R³ was explored. We found R¹ has no significant effect in the parallel synthesis. However, R² and R³ have to be aromatic groups; otherwise the reductive amination reactions are not clean and the isocyanates/isothiocyanates reactions and sequential cyclizations to form hydantoins/thiohydantoins are slow under our conditions. Two fluororous amino esters with different R¹, 6 aromatic aldehydes (R²), and 10 isocyanates or isothiocyanates (R³) were selected as building blocks. Their structures are listed in Scheme 3.

The fluororous tagged amino esters were readily prepared by reacting Fmoc-protected amino acids with a fluororous alcohol containing a C₈F₁₇ (Rf₈) chain under standard conditions using DIC and HOBt as coupling agents (Scheme 4). The perfluoroalkyl moiety is separated from the hydroxyl group by a propylene spacer to minimize the electronic effect of the fluororous tag. Deprotection of the Fmoc group with 1:3 piperidine/THF provided fluororous amino esters **1**. Both reaction steps were carried out under conventional solution-phase conditions. Compounds **5** and **1** can be purified by F-SPE or flash column chromatography with normal silica gel. Fluororous amino esters **1** can also be prepared using Boc-protected amino acids as starting materials.

Reductive amination reactions were performed in scintillation vials at room temperature followed by a quick aqueous workup. Intermediates **2** were purified by SPE over FluoroFlash™ cartridges. The non-fluororous byproducts and unreacted aldehydes were collected in the first fraction of 80:20 MeOH/H₂O, while fluororous products were collected in the second fraction of 100% MeOH. To achieve the best SPE separation, fluororous amino esters **1** were used as the limiting agents so that amines **2** were the only fluororous compounds in the reaction mixtures. In several cases, a small amount of di-*N*-alkylation compounds were observed as byproducts due to the presence of excess aldehydes and they were collected in 100% MeOH fraction along with the desired mono-*N*-alkylation products. At the next step of the isocyanate reaction, the byproducts remain unchanged since they cannot be converted to

urea **3** and undergo cyclization to form the hydantoins. The di-*N*-alkylated compounds were retained on the fluorous silica gel during the first F-SPE eluted with 80:20 MeOH/H₂O and thus separated from the final products.

At the isocyanate/isothiocyanate addition step, twelve intermediates **2** were split to 10 portions and underwent 120 parallel reactions. The urea/thiourea formation and sequential cyclization were fast and the reaction mixtures were directly loaded on FluoroFlash™ cartridges for SPE without workup. The non-fluorous final products were collected in the first fraction of 80:20 MeOH/H₂O, while the cleaved fluorous species, unreacted fluorous amines **2**, di-*N*-alkylation byproducts and ureas **3** (if any) were retained by the fluorous silica gel. Isocyanate/isothiocyanates were used as limiting agents so that products **4** and Et₃N were the only non-fluorous compounds collected in the 80:20 MeOH/H₂O fraction during SPE purification. Et₃N that co-eluted with the products was removed under vacuum during concentration. Typical ¹H NMR spectra of one of the final products before and after F-SPE are shown in Figure 1.

The amount of the final products was targeted at a 30 mg scale. LC-MS analysis revealed that 88% of the 120 products had purities >90% and 90% of the products had overall yields (last step) >50%. Structures, yields, and purities of 15 representative final products are listed in Scheme 5. Products **4**{**2,5,2**} and **4**{**2,6,2**} are axially chiral molecules because the methyl group at the *ortho* position restricted the free rotation of the C-N bond. They were detected as diastereomeric mixtures by ¹H NMR at room temperature.

In summary, we have demonstrated the utility of the fluorous parallel synthesis in the preparation of a library containing 120 hydantoin and thiohydantoin analogs. The purification was performed by parallel F-SPE. Neither fluorous solvent nor chromatography was needed for the separation of reaction mixtures.

3. Experimental

Fluorous alcohol C₈F₁₇CH₂CH₂CH₂OH was available from FTI [61]. Building blocks and reagents were obtained from commercial sources. SPE purification was conducted on a 2x12 SPE manifold available from Supelco and Fisher. NMR spectra were obtained on a Bruker AC-270 spectrometer (270 MHz). CDCl₃ was used as the solvent unless specifically mentioned. LC-MS spectra were obtained on an Agilent 1100 system.

General SPE procedures

A mixture containing fluorous and non-fluorous compounds in a minimum amount of solvent (< 20% of cartridge volume) is loaded onto a FluoroFlash™ cartridge [61] preconditioned with 80:20 MeOH/H₂O. The cartridge is eluted with 80:20 MeOH/H₂O (2–5 cartridge volume) for the non-fluorous compound(s) followed by same amount of MeOH for the fluorous compound (s). The loading of a SPE cartridge is around 5–10%. The cartridge can be reused by washing thoroughly with acetone or THF.

Preparation of amino ester **1**{**1**}

A solution of *N*-Fmoc-L-Leucine (5.30 g, 15 mmol, 1.5 equiv), perfluorooctylpropyl alcohol (4.78 g, 10 mmol, 1.0 equiv), DIC (2.34 mL, 15 mmol, 1.5 equiv), HOBT (2.03 g, 15 mmol, 1.5 equiv) and DMPA (0.12 g, 1.0 mmol, 0.1 equiv) in DMF (20 mL) were stirred overnight at room temperature. The reaction mixture was poured into ice (150 mL) and stirred for 5 min. The solution was decanted and the residue was washed with water one more time. To the residue was then added 20:80 EtOAc/hexane and stirred for 5 min. The white solid was filtered and washed with 20:80 EtOAc/hexane and the filtrate was concentrated. The residue was loaded onto a plug of silica gel (600 g) and eluted with EtOAc/hexane (20:80, 500 mL, 30:80, 1000

mL). The fluororous amino ester **5{1}** was obtained as a white solid (7.35 g, 90%) after concentration. ¹H NMR δ (ppm): 0.78–1.18 (m, 6H), 1.38–1.85 (m, 3H), 1.88–2.32 (m, 4H), 4.03–4.31 (m, 3H), 4.31–4.58 (m, 3H), 5.12–5.23 (m, 1H), 7.18–7.46 (m, 4H), 7.46–7.68 (m, 2H), 7.68–7.88 (m, 2H); MS (APCI): 814 (M+1)⁺.

A solution of **5{1}** (7.3 g, 9.0 mmol, 1.0 equiv) in 1:3 pyridine/THF (20 mL) was stirred for 30 min and concentrated. The residue was subjected to column chromatography on silica gel (eluted with 50:50 EtOAc/Hexane, 5:95 MeOH/EtOAc, 10:90 MeOH/EtOAc) to give **1{1}** (4.32 g, 90%) as light yellow oil. ¹H NMR δ (ppm): 0.93 (d, *J* = 4.8 Hz, 3H), 0.96 (d, *J* = 4.8 Hz, 3H), 1.38–1.68 (m, 4H), 1.68–1.84 (m, 1H), 1.92–2.08 (m, 2H), 2.08–2.32 (m, 2H), 3.50 (dd, *J* = 6.4, 9.4 Hz, 1H), 4.20 (t, *J* = 6.6 Hz, 2H); MS (APCI): 592 (M+1)⁺.

Preparation of amino ester **1{2}**

A solution of *N*-Boc-L-Phenylalanine (3.98 g, 15 mmol, 1.5 equiv), perfluorooctylpropyl alcohol (4.78 g, 10 mmol, 1.0 equiv), DIC (2.34 mL, 15 mmol, 1.5 equiv), HOBT (2.03 g, 15 mmol, 1.5 equiv) and DMPA (0.12 g, 1.0 mmol, 0.1 equiv) in DMF (20 mL) were stirred overnight at room temperature. The reaction mixture was poured into ice (150 mL) and stirred for 5 min. The solution was decanted and the residue was washed with water one more time. The residue was then added 20:80 EtOAc/hexane and stirred for 5 min. The white solid was filtered and washed with 20:80 EtOAc/hexane and the filtrate was concentrated. The residue was loaded onto a plug of silica gel (600 g) and eluted with EtOAc/hexane (20:80, 500 mL, 30:80, 1000 mL). The fluororous amino ester **5{2}** was obtained as a white solid (6.95 g, 95%) after concentration. ¹H NMR δ (ppm): 1.43 (s, 9H), 1.81–2.15 (m, 4H), 2.97–3.08 (m, 2H), 4.03–4.28 (m, 2H), 4.57 (q, *J* = 7.5 Hz, 1H), 4.98 (d, *J* = 6.0 Hz, 1H), 7.13–7.21 (m, 2H), 7.25–7.41 (m, 3H); MS (APCI): 726 (M+1)⁺.

A solution of **5{2}** (3.75 g, 5.17 mmol, 1.0 equiv) in 1:4 TFA/DCM (25 mL) was stirred for 2 hours and then concentrated. The residue was dissolved in DCM, basified with NaHCO₃ solution, washed with brine, dried over MgSO₄ and concentrated to give **1{2}** (3.80 g, 100%) as light yellow oil. ¹H NMR δ (ppm): 1.55–1.82 (br, 2H), 1.82–2.24 (m, 4H), 2.95 (dd, *J* = 15 Hz, 7.1 Hz, 1H), 3.07 (dd, *J* = 15 Hz, 6.8 Hz, 1H), 3.80 (t, *J* = 4.3 Hz, 1H), 4.05–4.23 (m, 2H), 7.15–7.43 (m, 5H); MS (APCI): 626 (M+1)⁺.

General procedure for reductive amination reactions

To a solution of fluororous amino ester **1** (1.0 equiv) in CH₂Cl₂ was added the aldehyde (1.1 equiv) in CH₂Cl₂. After stirring for 5 min, NaBH(OAc)₃ (1.2 equiv) was added and the reaction mixture was stirred for 1 hour before quenching with water and NH₄OH. The mixture was extracted with CH₂Cl₂ and the combined organic solution was dried and concentrated. The residue was dissolved in CH₂Cl₂ (1.0 mL) and loaded onto a FluoroFlash^{TM} cartridge (10.0 g). The cartridge was eluted with 80:20 MeOH/H₂O (2x16 mL) and then MeOH (3x16 mL). The MeOH fractions were combined and concentrated to afford **2** as a white solid.

Analytical data for **2{1,1}**

¹H NMR δ (ppm): 0.87 (d, *J* = 7.3 Hz, 3H), 0.93 (d, *J* = 7.3 Hz, 3H), 1.40–1.57 (m, 2H), 1.68–1.87 (m, 2H), 1.90–2.33 (m, 4H), 3.33 (t, *J* = 8.2 Hz, 1H), 3.64 (d, *J* = 15 Hz, 1H), 3.83 (d, *J* = 15 Hz, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 7.23–7.38 (m, 5H); MS (APCI): 682 (M+1)⁺.

Analytical data for **2{2,1}**

¹H NMR δ (ppm): 1.70–2.08 (m, 5H), 2.94 (dd, *J* = 15 Hz, 8.6 Hz, 1H), 3.08 (dd, *J* = 15 Hz, 7.2 Hz, 1H), 3.60 (t, *J* = 7.9 Hz, 1H), 3.71 (d, *J* = 15 Hz, 1H), 3.86 (d, *J* = 15 Hz, 1H), 3.95–4.18 (m, 2H), 7.13–7.44 (m, 10H); MS (APCI): 716 (M+1)⁺.

General procedure for the preparation of hydantoins/thiohydantoins 4

To a solution of **2** (1.1 equiv) in CH₂Cl₂ was added isocyanate or isothiocyanate (1.0 equiv) and Et₃N (1.0 equiv). The reaction mixture was stirred for 1 hour at room temperature and loaded directly onto a FluoroFlash™ cartridge (2 g). The cartridge was eluted with 80:20 MeOH/H₂O (2x6 mL) and then acetone (2x6 mL). The 80:20 MeOH/H₂O fractions were combined and concentrated to give **4** as a white solid.

Analytical data for 4{1,1,1}

¹H NMR δ (ppm): 0.90 (d, *J* = 7.3 Hz, 3H), 0.95 (d, *J* = 7.3 Hz, 3H), 1.76–1.87 (m, 2H), 1.87–2.07 (m, 1H), 3.93 (t, *J* = 6.0 Hz, 1H), 4.13 (d, *J* = 16.8 Hz, 1H), 5.19 (d, *J* = 16.8 Hz, 1H), 7.26–7.58 (m, 10H); MS (APCI): 323 (M+1)⁺.

Analytical data for 4{1,2,3}

¹H NMR δ (ppm): 0.91 (d, *J* = 7.3 Hz, 3H), 0.96 (d, *J* = 7.3 Hz, 3H), 1.76–1.87 (m, 2H), 1.87–2.07 (m, 1H), 2.37 (s, 3H), 2.42 (s, 3H), 3.91 (t, *J* = 6.0 Hz, 1H), 4.06 (d, *J* = 16.8 Hz, 1H), 5.17 (d, *J* = 16.8 Hz, 1H), 7.16–7.30 (m, 7H), 7.36 (t, *J* = 8.4 Hz, 1H); MS (APCI): 351 (M+1)⁺.

Analytical data for 4{1,3,5}

¹H NMR δ (ppm): 0.90 (d, *J* = 7.3 Hz, 3H), 0.95 (d, *J* = 7.3 Hz, 3H), 1.76–1.87 (m, 2H), 1.87–2.07 (m, 1H), 3.95 (t, *J* = 6.0 Hz, 1H), 4.13 (d, *J* = 16.8 Hz, 1H), 5.09 (d, *J* = 16.8 Hz, 1H), 7.21 (d, *J* = 9.3 Hz, 2H), 7.53 (d, *J* = 9.3 Hz, 2H), 7.64 (d, *J* = 9.6 Hz, 2H), 7.74 (d, *J* = 9.6 Hz, 2H); MS (APCI): 469 (M+1)⁺, 471 (M+3)⁺.

Analytical data for 4{1,4,7}

¹H NMR δ (ppm): 0.89 (d, *J* = 7.3 Hz, 3H), 0.95 (d, *J* = 7.3 Hz, 3H), 1.76–1.87 (m, 2H), 1.87–2.07 (m, 1H), 3.81 (s, 3H), 3.90 (t, *J* = 6.0 Hz, 1H), 4.04 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.37 (dd, *J* = 2.7, 9.6 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.65 (d, *J* = 2.7 Hz, 1H); MS (APCI): 421 (M+1)⁺, 423 (M+3)⁺.

Analytical data for 4{1,5,9}

¹H NMR δ (ppm): 0.96 (d, *J* = 7.3 Hz, 3H), 0.99 (d, *J* = 7.3 Hz, 3H), 1.88–2.07 (m, 3H), 2.40 (s, 3H), 4.19 (t, *J* = 6.0 Hz, 1H), 4.49 (d, *J* = 16.8 Hz, 1H), 5.76 (d, *J* = 16.8 Hz, 1H), 6.36–6.49 (m, 2H), 7.18 (d, *J* = 9.3 Hz, 2H), 7.30 (d, *J* = 9.3 Hz, 2H), 7.43 (d, *J* = 1.2 Hz, 1H); MS (APCI): 343 (M+1)⁺.

Analytical data for 4{1,6,9}

¹H NMR δ (ppm): 0.91 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.88–2.07 (m, 3H), 2.42 (s, 3H), 3.93 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 1H), 4.43 (d, *J* = 16.8 Hz, 1H), 6.04 (d, *J* = 16.8 Hz, 1H), 7.18–7.28 (m, 2H), 7.30–7.47 (m, 5H), 7.54–7.63 (m, 2H), 7.77–7.87 (m, 2H); MS (APCI): 441 (M+1)⁺.

Analytical data for the major diastereomer of 4{2,6,2}

¹H NMR δ (ppm): 2.19 (s, 3H), 3.19–3.43 (m, 2H), 3.93 (s, 2H), 4.15–4.35 (m, 2H), 5.39 (d, *J* = 13.5 Hz, 1H), 7.09–7.49 (m, 13H), 7.54–7.65 (m, 1H), 7.73–7.90 (m, 2H); MS (APCI): 459 (M+1)⁺.

Analytical data for the major diastereomer of 4{2,5,2}

^1H NMR δ (ppm): 2.18 (s, 3H), 3.20–3.33 (m, 2H), 4.18–4.39 (m, 2H), 5.13 (d, $J = 17.4$ Hz, 1H), 6.26–6.42 (m, 2H), 7.07–7.41 (m, 9H), 7.41–7.50 (m, 1H); MS (APCI): 361 (M+1) $^+$.

Analytical data for 4{2,4,4}

^1H NMR δ (ppm): 2.35 (s, 3H), 3.16–3.33 (m, 2H), 3.85 (s, 3H), 4.03 (d, $J = 16.6$ Hz, 1H), 4.16 (t, $J = 5.0$ Hz, 1H), 5.18 (d, $J = 16.6$ Hz, 1H), 6.89 (d, $J = 9.3$ Hz, 2H), 6.95 (d, $J = 9.3$ Hz, 2H), 7.13–7.25 (m, 6H), 7.28–7.38 (m, 3H); MS (APCI): 401 (M+1) $^+$.

Analytical data for 4{2,4,6}

^1H NMR δ (ppm): 2.47 (s, 3H), 3.16–3.33 (m, 2H), 3.82 (s, 3H), 4.04 (d, $J = 16.6$ Hz, 1H), 4.16 (t, $J = 5.0$ Hz, 1H), 5.17 (d, $J = 16.6$ Hz, 1H), 6.89 (d, $J = 9.3$ Hz, 2H), 6.95 (d, $J = 9.3$ Hz, 2H), 7.07–7.38 (m, 9H); MS (APCI): 433 (M+1) $^+$.

Analytical data for 4{2,3,6}

^1H NMR δ (ppm): 2.47 (s, 3H), 3.16–3.33 (m, 2H), 4.04 (d, $J = 16.8$ Hz, 1H), 4.16 (t, $J = 5.1$ Hz, 1H), 5.17 (d, $J = 16.8$ Hz, 1H), 6.96–7.10 (m, 4H), 7.10–7.21 (m, 2H), 7.10–7.87 (m, 5H), 7.49 (d, $J = 9.3$ Hz, 2H); MS (APCI): 481 (M+1) $^+$, 483 (M+3) $^+$.

Analytical data for 4{2,3,8}

^1H NMR δ (ppm): 3.24 (dd, $J = 16.2$ Hz, 5.3 Hz, 1H), 3.37 (dd, $J = 16.2$ Hz, 4.6 Hz, 1H), 4.32 (t, $J = 5.0$ Hz, 1H), 4.37 (d, $J = 16.8$ Hz, 1H), 5.97 (d, $J = 16.8$ Hz, 1H), 6.84–6.95 (m, 1H), 7.12–7.26 (m, 4H), 7.20–7.48 (m, 7H), 7.48–7.59 (m, 2H); MS (APCI): 451 (M+1) $^+$, 453 (M+3) $^+$.

Analytical data for 4{2,2,8}

^1H NMR δ (ppm): 2.39 (s, 3H), 3.24 (dd, $J = 15.9$ Hz, 4.8 Hz, 1H), 3.37 (dd, $J = 15.9$ Hz, 4.6 Hz, 1H), 4.32 (t, $J = 4.6$ Hz, 1H), 4.38 (d, $J = 16.5$ Hz, 1H), 6.04 (d, $J = 16.5$ Hz, 1H), 6.84–6.92 (m, 1H), 7.17–7.29 (m, 6H), 7.30–7.48 (m, 7H); MS (APCI): 387 (M+1) $^+$.

Analytical data for 4{2,1,10}

^1H NMR δ (ppm): 3.16–3.33 (m, 2H), 4.12 (d, $J = 16.8$ Hz, 1H), 4.19 (t, $J = 4.8$ Hz, 1H), 5.24 (d, $J = 16.8$ Hz, 1H), 7.02–7.14 (m, 4H), 7.14–7.52 (m, 10H); MS (APCI): 375 (M+1) $^+$.

Analytical data for 4{2,2,10}

^1H NMR δ (ppm): 2.38 (s, 3H), 3.16–3.33 (m, 2H), 4.08 (d, $J = 16.8$ Hz, 1H), 4.18 (t, $J = 4.8$ Hz, 1H), 5.21 (d, $J = 16.8$ Hz, 1H), 7.00–7.11 (m, 4H), 7.11–7.25 (m, 6H), 7.25–7.40 (m, 3H); MS (APCI): 389 (M+1) $^+$.

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Abbreviations

Rf	perfluoroalkyl group
SPE	solid-phase extraction
DIC	1,3-diisopropylcarbodiimide
HOBT	1-hydroxybenzotriazole
Fmoc	9-fluorenylmethoxycarbonyl
Boc	<i>t</i> -butoxycarbonyl
THF	tetrahydrofuran

DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
HPLC	high-performance liquid chromatography
TLC	thin-layer chromatography
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
LC-MS	liquid chromatography-mass spectrometry
FTI	Fluorous Technologies, Inc

Figure 1.
 ^1H NMR (CDCl_3) spectra of product **4{2,2,8}** before and after F-SPE.

Hydantocidin

$R^1, R^2 = \text{H, Me}$
 $X = \text{O, NH, Y} = \text{H, Br}$

Aplysinopsins

Scheme 1.
Hydantoin related natural products

Scheme 2.
Fluorous synthesis of hadontoin analogs

2 aminoesters for different R¹

{1}

{2}

6 aldehydes for different R²

{1}

{2}

{3}

{4}

{5}

{6}

10 isocyanates/isothiocyanates for different R³

{1}

{2}

{3}

{4}

{5}

{6}

{7}

{8}

{9}

{10}

Scheme 3.

Building blocks for parallel synthesis.

Scheme 4.
Synthesis of fluororous amino esters **1**.

^a determined by LC-MS. ^bratio of diastereomers by ¹H NMR

Scheme 5.

Structures, yields, and purities^a of 15 representative final products **4{R¹,R²,R³}**.