Fluorous Synthesis of Substituted Sclerotigenin Library

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A fluorous linker-assisted synthetic protocol has been developed for preparation of sclerotigenin-type benzodiazepine-quinazolinone library containing 144 analogues. Amide coupling of fluorous trimethoxybenzyl (TMB)-protected amino esters with anthranilic acids followed by base-promoted cyclizations afforded 4-benzodiazepine-2,5-diones. Further derivatization of benzodiazepinediones by reacting with azidobenzoyl chlorides, cyclization, and fluorous linker cleavage afforded the desired compound library. The reaction intermediates were purified by fluorous solid-phase extraction (F-SPE) and final products were further purified by prep-HPLC.

Introduction

Natural alkaloid sclerotigenin was isolated from the sclerotia of *Penicillium sclerotigenum*.[1] It is the simplest compound in the family of benzodiazepine-quinazolinones. Sclerotigenin and other members in the family, such as circumdatins A-G isolated from the terrestrial fungus *Aspergillus ochraceus,*[2a] benzomalvins A-C isolated from the fungus *Penicillium* sp,[2b] and asperlicin derived from the fungus *Aspergillus alliaceus*,[2c] possess a wide range of biological activities (Scheme 1).[3] Sclerotigenin is an attractive library scaffold for production of substituted analogues for biological screening.

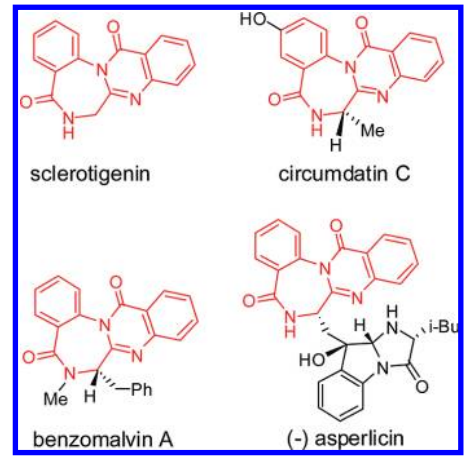
1,4-Benzodiazepine-2,5-dione is a privileged ring system which can be found in numerous biological active compounds.[4] In the current project, 1,4-benzodiazepine-2,5-dione is a key intermediate for the synthesis of benzodiazepine-quinazolinone alkaloids. In our continuous effort of developing fluorous linker-facilitated synthesis of drug-like and natural product analogues,[5,6] we have introduced different methods for the preparation of benzodiazepine-2,5-diones.[7] Report here is the synthesis of benzodiazepinedione scaffold using fluorous trimethoxybenzyl (TMB)-type linker to facilitate intermediate purification by fluorous solid-phase extraction (F-SPE).[8,9] A general synthetic route for library synthesis is highlighted in Scheme 2. The synthesis started with the coupling of fluorous TMB-protected amino esters **1** with anthranilic acids **2** to afford amides **3**. Base-promoted cyclizations of **3** yielded 4-benzodiazepine-2,5-diones **4**. *N*-Acylation of benzodiazepinediones with azidobenzoyl chlorides **5** gave compounds **6**. The reductions of the azido group and subsequent cyclization afforded compounds **7**. Final products **8** were obtained by cleavage of the fluorous linker. A library containing 144 compounds were prepared from four F-TMB-protected amino esters **1**, four anthranilic acids **2**, and nine 2-azidobenzoyl chlorides **5.** All the reaction intermediates were purified by F-SPE. The final products were treated with F-SPE, then followed by prep-HPLC to ensure >90% purity for biological screening.

Results and Discussion

A number of conventional solution-phase and solid-phase synthetic protocols for benzodiazepines have been reported in the literature.[10] We modified the solid-phase method developed by the Ellman group and used F-TMB-type linker for fluorous synthesis.[11] F-TMB-type linker was readily prepared by the reaction of 4-hydroxy-2,6-dimethoxybenzaldehyde with 3-(perfluorooctyl)propyl iodide. F-TMB was attached to four different amino esters by reductive amination to produce compounds **1**{*1*−*4*} (Scheme 3).

Four F-TMB-attached amino esters **1**{*1*−*4*} in *N*-methylpyrrolidine (NMP) were reacted with four anthranilic acids **2**{*1*−*4*} in the presence of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI) to form sixteen amide coupling products **3**{R^1,R^2} (Scheme 4). The 1,4-benzodiazepine-2,5-

Scheme 1. Sclerotigenin-Type Benzodiazepine-Quinazolinone Natural Products



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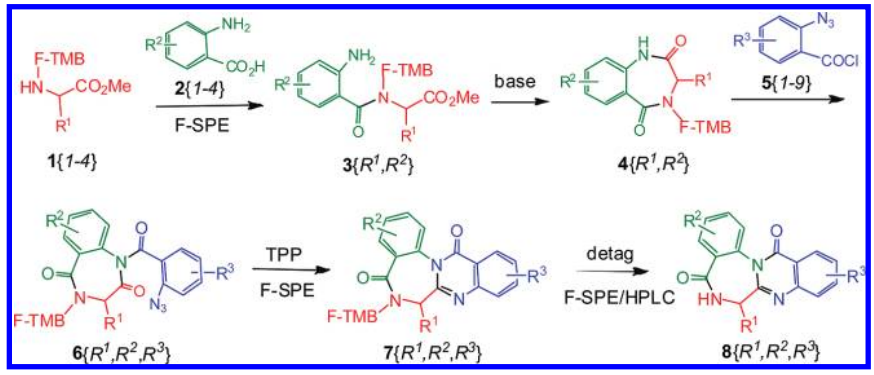
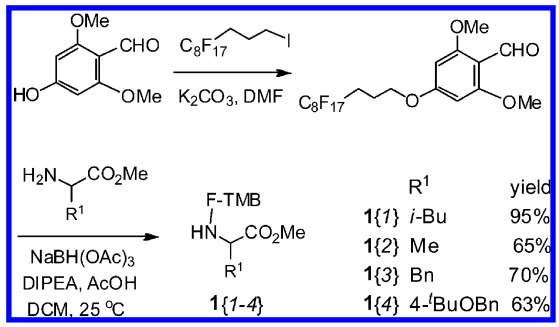
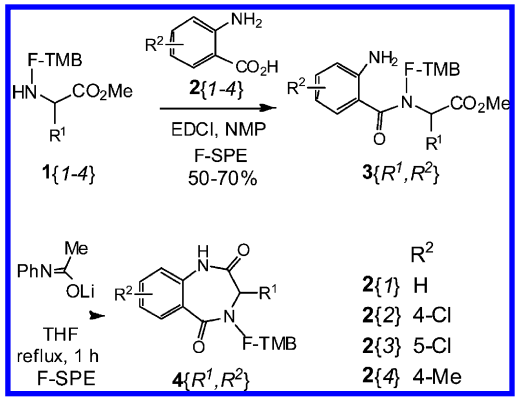
Scheme 2. Proposed Synthetic Route for Sclerotigenin-Type Benzodiazepine-Quinazolinones



Scheme 3. Synthesis of F-TMB and Attached Amino Esters **1**{*1*−*4*}



Scheme 4. Synthesis of 1,4-Benzodiazepine-2,5-dione **4**{*1*−*4*,*1*−*4*}



dione ring formation was accomplished by base-promoted cyclization of **3** in heated tetrahydrofuran (THF). Sixteen 1,4-benzodiazepine-2,5-dione analogues **4**{*1*−*4*,*1*−*4*} with substitution variations at R^1 and R^2 were prepared with >90% purity. The yields of the cyclization products after recrystallization are listed in Table 1.

The next step of the library synthesis was the reactions of 16 1,4-benzodiazepine-2,5-dione analogues **4**{*1*−*4*,*1*−*4*} with 9 different azidobenzoyl chlorides **5**{*1*−*9*} to generate 144 *N*-acylated products **6**{*1*−*4*,*1*−*4*,*1*−*9*} (Scheme 5). Compounds **4** in THF were treated with BuLi at −78 °C, warmed up to room temperature, and then mixed with azidobenzoyl chlorides **5**. MeOH was added to quench the reactions to give *N*-acylated products **6**. The resulting crude mixture was concentrated and used for the next step without further purification. In the cyclization step to form the core of sclerotigenin, compounds **6** in CH_2Cl_2 were treated with triphenylphosphine (TPP) at room temperature for 3 h. The reaction mixtures were purified by automatic F-SPE on the RapidTrace system.[9b] In this step, we found reactions with R^1 = Me did not afford products **6**{*1*−*4*}. The last step of fluorous linker cleavage was accomplished by the treatment of compounds **7** with 90:5:5 TFA/DMS/H_2O at room temperature for 3 days. The concentrated reaction mixtures were purified by automatic F-SPE on the RapidTrace system followed by prep-HPLC. Yields and purities of the final products are listed in Table 2. After F-SPE the purity of the final products were in the range of 50−70%. After prep-HPLC separation only compounds have >90% purities were collected and submitted for biological test.

Table 1. Yields and Purities of Sixteen 1,4-Benzodiazepine-2,5-diones **4**{*1*−*4*,*1*−*4*}

entry	**4**{R^1,R^2}	yield
1	**4**{*1*,*1*}	57%
2	**4**{*1*,*2*}	69%
3	**4**{*1*,*3*}	69%
4	**4**{*1*,*4*}	44%
5	**4**{*2*,*1*}	54%
6	**4**{*2*,*2*}	59%
7	**4**{*2*,*3*}	56%
8	**4**{*2*,*4*}	60%
9	**4**{*3*,*1*}	64%
10	**4**{*3*,*2*}	42%
11	**4**{*3*,*3*}	45%
12	**4**{*3*,*4*}	55%
13	**4**{*4*,*1*}	73%
14	**4**{*4*,*2*}	88%
15	**4**{*4*,*3*}	87%
16	**4**{*4*,*4*}	86%

Scheme 5. Synthesis of Substituted Sclerotigenin **8**{*1*−*4*,*1*−*4*,*1*−*9*}

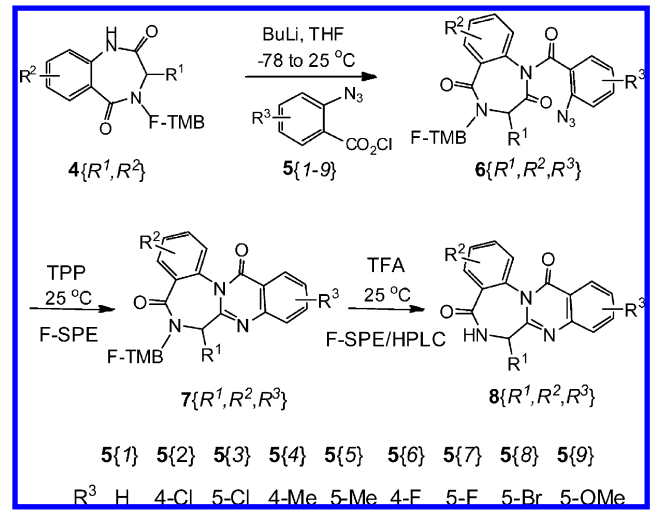


Table 2. Yields [%] (Purity UV220 [%]) of Final Products **8**{*1−4,1−4,1−9*}

(a) Products **8**{*1,1−4,1−9*}

8{*1,R²,R³*}	**2**{*1*}	**2**{*2*}	**2**{*3*}	**2**{*4*}
5{*1*}	15 (92)	11 (9)	15 (90)	17 (92)
5{*2*}	21 (92)	15 (90)		14 (93)
5{*3*}	16 (93)	18 (92)		16 (92)
5{*4*}	16 (92)	14 (92)		12 (93)
5{*5*}	14 (92)	12 (91)	11 (90)	9 (92)
5{*6*}	23 (91)	19 (92)	14 (92)	9 (91)
5{*7*}	21 (92)	17 (93)	18 (92)	9 (93)
5{*8*}	19 (93)	12 (93)	15 (92)	8 (92)
5{*9*}		15 (93)		

(b) Products **8**{*2,1−4,1−9*}

8{*2,R²,R³*}	**2**{*1*}	**2**{*2*}	**2**{*3*}	**2**{*4*}
5{*1*}				
5{*2*}			11 (95)	
5{*3*}				
5{*4*}				
5{*5*}				
5{*6*}	38 (98)		12 (95)	10 (98)
5{*7*}	13 (97)			9 (98)
5{*8*}				10 (98)
5{*9*}	10 (95)			11 (98)

(c) Products **8**{*3,1−4,1−9*}

8{ *3,R²,R³*}	**2**{*1*}	**2**{*2*}	**2**{*3*}	**2**{*4*}
5{*1*}	11 (91)	27 (95)	22 (95)	19 (90)
5{*2*}	18 (95)	17 (93)	5 (97)	13 (90)
5{*3*}	15 (90)	24 (96)	23 (95)	15 (92)
5{*4*}	13 (92)	23 (95)	18 (94)	19 (91)
5{*5*}	23 (94)	22 (95)	24 (96)	18 (91)
5{*6*}	20 (93)	29 (93)	21 (97)	22 (91)
5{*7*}	18 (92)	18 (93)		
5{*8*}	11 (91)	17 (96)	15 (90)	
5{*9*}	16 (91)	14 (90)	15 (92)	

(d) Products **8**{*4,1−4,1−9*}

8{ *4,R²,R³*}	**2**{*1*}	**2**{*2*}	**2**{*3*}	**2**{*4*}
5{*1*}	16 (91)	14 (94)		14 (91)
5{*2*}	10 (94)	9 (92)	10 (93)	10 (93)
5{*3*}	11 (94)	14 (95)	15 (96)	12 (93)
5{*4*}	11 (91)	15 (91)	10 (93)	11 (92)
5{*5*}	18 (91)	19 (92)	16 (90)	16 (91)
5{*6*}	21 (93)	14 (92)	14 (94)	18 (93)
5{*7*}	11 (92)	8 (90)		11 (93)
5{*8*}	5 (93)		14 (95)	11 (92)
5{*9*}	11 (92)		9 (90)	16 (90)

Conclusions

With the assistance of fluorous TMB linker and F-SPE for intermediate purification and final product pre-purification, a library containing 144 sclerotigenin analogues was synthesized. Among them, 103 final products were obtained with greater than 90% purity. Ninety-two compounds have been submitted to NIH repository and are currently being evaluated in several high-throughput screening programs. Results on their biological activities can be found in PubChem (http://pubchem.ncbi.nlm.nih.gov).

Experimental Section

General Information. All fluorous reagents and silica gel (40−60 μm particle size) used in this project are available from Fluorous Technologies, Inc.[12] Other reagents and solvents were obtained from commercial sources. The RapidTrace SPE system was purchased from Caliper Life Sciences. One drum vials were used for all the reactions. Preparative HPLC were performed on a Waters Delta Prep system. LC-MS spectra were obtained on an Agilent 1100 system. Genevac EZ-2 vacuum centrifuge was used for solvent evaporation. Products purities were determined by LC-MS with a C_{18} column.

General Procedures for the Synthesis of F-TMB-Attached Amino Esters 1{*1−4*}. To a solution of amino ester hydrochloride (42 mmol), 2,6-dimethoxy-4-[3-(perfluorooctyl)propyloxy]benzaldehyde (40 mmol), *N*,*N*-diisopropylethylamine (40 mmol), and acetic acid (1 mL) in CH_2Cl_2 (300 mL) was added 4 Å molecular sieves (3 g) at 25 °C. $NaBH(OAc)_3$ (60 mmol) was added after 4 h, and the reaction was quenched with water after an additional 3 h. The CH_2Cl_2 layer was washed with aq. NH_4Cl and brine. After most of the solvent was removed using a rotary evaporator, the residue was passed through a pad of silica gel (50 mL). The product was eluted with hexanes-EtOAc (1:1, 300 mL). The concentrated product was further triturated with hexanes-Et_2O to give the desired compound **1**. Analytical data for **1**{*1*}: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.08 (s, 2H), 4.02 (t, 2H, J = 5.8 Hz), 3.78 (s, 6H), 3.59 (s, 3H), 3.26 (t, 1H, J = 7.1 Hz), 2.45−2.00 (m, 5H), 1.82−1.35 (m, 3 H), 0.88 (d, 3H, J = 6.5 Hz), 0.81 (d, 3H, J = 6.4 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.4, 159.3, 108.9, 90.7, 66.3, 59.0, 55.5, 51.3, 42.8, 39.9, 28.2, 27.9, 27.5, 24.8, 22.6, 22.0, 20.5. LC-MS (ESI+) m/z 772 $[M+1]^+$.

General Procedures for Amide Coupling to Synthesize 3{*1−4,1−4*}. To a solution of **1** (5.6 mmol) in *N*-methylpyrrolidine (30 mL), anthranilic acid (11 mmol) and EDCI-HCl (11 mmol) were added as solids at 23 °C. The same amounts of the acid and EDCI-HCl were added after 2 and 4 h. One day after the final addition, the reaction mixture was diluted with DMSO (400 mL) and loaded onto an F-SPE cartridge (50 g). The non-fluorous components were eluted with MeCN-H_2O (1:1, 300 mL, and 4:1, 200 mL) and most of the solvent was drained. The amide coupling product was eluted with MeCN (400 mL). The MeCN fraction was concentrated to give desired compounds, and product purities was checked by LC-MS analysis. The crude products were used for next step reactions without further purification.

General Procedures for Base-Promoted Cyclization to Synthesize 4-Benzodiazepine-2,5-diones 4{*1−,1−4*}. A solution of **3** (5 mmol) in THF was treated with a solution of lithium acetanilide (0.33 M in THF, 30 mL). The mixture was refluxed for 1 h. After cooling, AcOH (0.6 mL) was added, and the solvent was removed in a rotary evaporator. MeOH (30 mL) was added to the residue, and it was heated until the solvent started to boil. The mixture was left at 25 °C for 1 d, and product **4** was obtained as white solid after filtration. Analytical data for **4**{*1,2*}: ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.16 (dd, J = 7.1, 1.9 Hz 1,), 6.90 (d, J = 1.8 Hz, 1H), 6.09 (s, 2H), 5.23 (d, J = 13.8 Hz, 1H), 4.56 (d, J = 13.8 Hz, 1H), 4.15−3.85 (m, 3H), 3.75 (s, 6H), 2.45−2.00 (m, 4H), 1.60−1.45 (m, 1H), 1.35−1.15 (m, 2H), 0.80 (d, J = 6.4 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H). ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 173.5, 165.1, 160.6, 160.1, 137.7, 136.2, 133.3,

125.5, 124.6, 119.4, 104.1, 90.6, 66.3, 59.5, 55.5, 42.0, 38.3, 27.9 (t, J = 22 Hz), 25.2, 22.3, 22.1, 20.5. LC-MS (ESI +) m/z 893 $[M+1]^+$.

General Procedures for N-Acylation to Synthesize 6{*1*−*4*}. Benzodiazopinone **4** (0.9 mmol) in THF (10 mL) was cooled to −78 °C and BuLi (1.6M, 1.1 mL, 1.8 mmol) was added dropwise. The reaction mixture was warmed to 25 °C and distributed to a row of 9 vials containing azobenzoylchlorides **5**{*1*−*9*} (0.4 mmol) in DCM (0.4 mL). The vials were shaken at 25 °C for 3 h before MeOH (0.5 mL) was added to each vial. The reaction mixtures were left to stand overnight and concentrated. LC-MS analysis indicated that most reactions where R^1 = Me did not afford products **6**{*1*−*4*}. The crude products were used for next step without further purification.

General Procedures for Reduction and Cyclization to Synthesize 7{*1*−*4*}. The crude intermediates **6**{*1*−*4*} in DCM (1 mL) were added TPP (0.4 mmol) in DCM (1 mL), and the reaction mixtures were shaken at 25 °C for 3 h before being concentrated. The residues were dissolved in DMF (0.7 mL) and purified by RapidTrace FSPE (2 g). The elution sequence was as follows: loading (1 mL), rinsing with DMF/H_2O (9:1) (1 mL), eluting with DMF/H_2O (9:1) 6 mL, air-dry (6 mL), eluting with MeOH (6 mL, collected) and MeOH/THF/TFA (12 mL). The MeOH fraction was concentrated to give crude products, and their purities were checked by LC-MS analysis. The crude products **7**{*1*−*4*} were used for the next step without further purification.

General Procedures for Fluorous Linker Cleavage and Final Product Purification. The crude intermediates **7**{*1*−*4*} were dissolved in TFA/DMS/H_2O (90:5:5) (1 mL), and the mixture was shaken for 3 days, evaporated over 2 days, and concentrated. The residue was dissolved in DMF (0.7 mL) and purified by RapidTrace FSPE (2 g). The elution sequence was as follows: loading (1 mL, collected), rinsing with DMF/H_2O (9:1) (1 mL, collected), eluting with DMF/H_2O (9:1) (4 mL, collected), and MeOH/THF/TFA (12 mL). The collected fraction (DMF/H_2O) was concentrated and analyzed by LC-MS. Preparative HPLC afforded the pure products **8** in 5−20% yield for 3 steps. Analytical data for **8**{*1*,*2*,*1*}: ^{1}H NMR (275 Hz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 1.80−2.05 (m, 2H), 2.05−2.25 (m, 1H), 4.10−4.35 (m, 1H), 6.66 (d, J = 6.2 Hz, 1H), 7.45−7.59 (m, 2H), 7.67 (d, J = 1.9 Hz, 1H), 7.70−7.85 (m, 2H), 7.91 (d, J = 8.4 Hz, 1H), 8.31 (dd, J = 1.4, 8.0 Hz, 1H); ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 22.0, 23.1, 24.3, 38.0, 52.4, 121.3, 127.5, 127.8, 127.9, 128.7, 128.9, 129.5, 131.0, 134.3, 135.2, 137.4, 146.0, 154.1, 161.5, 167.1; LC-MS (ESI+) 368 $[M+1]^+$.

Supporting Information Available. LC-MS spectra of purified final products and ^{1}H NMR spectra of representative final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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