Use of Cyclohexylisocyanide and Methyl 2-Isocyanoacetate as Convertible Isocyanides for Microwave-Assisted Fluorous Synthesis of 1,4-Benzodiazepine-2,5-dione Library

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A new protocol in which cyclohexylisocyanide and methyl 2-isocyanoacetate are used as convertible isocyanides for Ugi/de-Boc/cyclization/Suzuki synthesis of biaryl-substituted 1,4-benzodiazepine-2,5-diones has been developed. Ugi reactions of Boc-protected anthranilic acids, fluorous benzaldehydes, amines, and cyclohexylisocyanide or methyl 2-isocyanoacetate were carried out at room temperature. Microwave-promoted de-Boc/cyclization reactions afforded 1,4-benzodiazepine-2,5-diones (BZDs). Suzuki coupling reactions further derivatized the BZD ring by removing the fluorous tag and introducing the biaryl group. A thirty three-member biaryl-substituted BZD library containing four points of diversity was prepared by microwave-assisted solution-phase fluorous parallel synthesis.

Introduction

The synthesis of 1,4-benzodiazepine-2,5-diones (BZDs) has received much attention because of their wide range of biological utilities.[1−4] Multicomponent reactions (MCRs) such as Ugi four-component reactions have been employed for the construction of BZD scaffolds.[5−12] MCRs have the capability to build target scaffolds with maximal substitution diversities through a simple reaction process.[13−15] MCR-based strategy has been developed for solution phase,[5] solid phase,[16−19] ionic liquid,[20] and fluorous synthesis[21] of BZD scaffolds.

In 1996 the Armstrong group introduced 1-isocyanocyclohexene as a convertible isocyanide for Ugi reactions.[22,23] This convertible isocyanide has been used in the Ugi/de-Boc/cyclization synthesis of BZDs (Scheme 1, top).[4,24−27] The cleavage of cyclohexenylamino group from the amide bond occurs through the formation of an oxazolinium-5-one intermediate followed by a nucleophilic reaction with the amino group.[23,28−30] The utility of 1-isocyanocyclohexene is limited because it is not commercially available and not so convenient to prepare in house. Commercially available cyclohexylisocyanide[31−33] and methyl 2-isocyanoacetate[18] have been used for Ugi reactions. But because of cyclohexylamino and methylacetylamino groups are relatively stable and not so easy to cleave, they are generally used as non-convertible isocyanides. We have employed cyclohexylisocyanide in the fluorous parallel synthesis of a BZD library.[21] The de-Boc/cyclization occurred between the amino and ester groups instead of the amino and amide groups (Scheme 1, bottom).

Reported in this paper is a new method to synthesize BZDs using the Ugi/de-Boc/cyclization approach. It was developed based on our recent discovery of using cyclohexylisocyanide and methyl 2-isocyanoacetate as convertible isocyanides. We have found that under microwave irradiation for 20 min at 150 °C, de-Boc/cyclization occurred between the amino group and the amide bonds (Scheme 2, bottom). However, under conventional heating of refluxing MeOH at 70 °C for 12 h, only deprotected product was detected by LC-MS analysis (Scheme 2, top).

Results and Discussion

The Ugi/de-Boc/cyclization using cyclohexylisocyanide or methyl 2-isocyanoacetate as convertible isocyanides is highlighted in Scheme 3. The first step of Ugi condensation was performed at room temperature in MeOH using Boc-protected anthranilic acid **1a**, 4-chlorobenzaldehyde **2a**, piperonylamine **3a**, and cyclohexylisocyanide **4a** (Scheme 3). The precipitate formed at the beginning of the reaction disappeared after stirring at room temperature for 24 h. The reaction mixture turning to clear is an indication of completion which was confirmed by LC-MS analysis. The Ugi product **5a** was isolated in 75% yield. The reaction could be finished in 10 h if conducted at 50 °C and gave **5a** in 88% yield. For the de-Boc/cyclization reaction, 1:1 TFA-MeOH was found to be an optimal ratio. The reaction was completed in 20 min at 150 °C under microwave irradiation to afford product **6a** in 63% yield. When methyl 2-isocyanoacetate was used for Ugi reaction, product **5b** was isolated in 91% yield, and the cyclization product **6a** was isolated in 59% yield.

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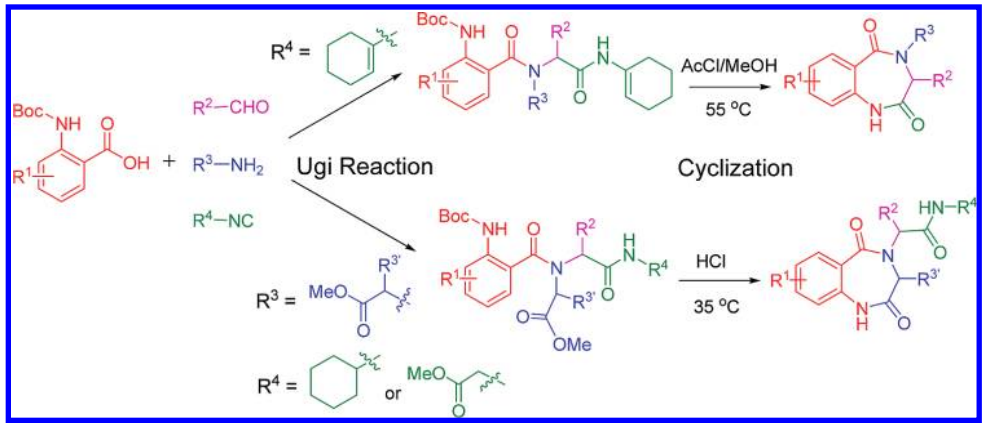
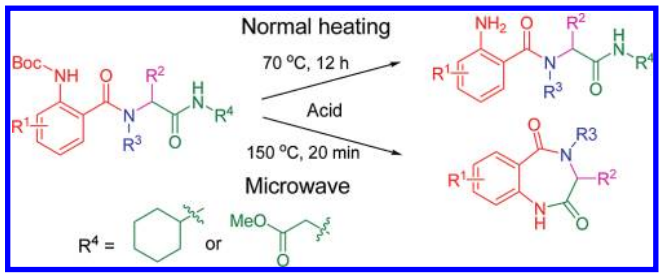
Scheme 1. Ugi/de-Boc/Cyclization Synthesis of BZDs



Scheme 2. Microwave-Assisted Synthesis of BZDs



We next extended the Ugi/de-Boc/cyclization reactions for fluorous parallel synthesis of BZDs **6**. Two fluorous benzaldehydes **2**{***1***−***2***},[21,34−37] five Boc-protected anthranilic acids **1**{***1***−***5***},[38−40] five amines **3**{***1***−***5***}, and two isocyanides **4**{***1***−***2***} were used for Ugi reactions (Scheme 4). During the reaction validation, we found that Ugi reaction with **1**{***5***} failed, probably because of the low solubility of **1**{***5***} in MeOH. The introduction of the fluorous tag in general did not affect the reactivity of aldehydes. The optimal ratio of **1:2:3:4** for Ugi reactions was found to be 1.25:1:1.25:1.25 through a series of optimizations. A slightly excess of non-fluorous components was used to consume fluorous aldehyde **2** and make fluorous Ugi (F-Ugi) product **5** as the only fluorous compound in the reaction mixture. In this way **5** can be easily purified by fluorous solid-phase extraction (F-SPE). The excess non-fluorous starting materials and byproducts were removed by F-SPE and collected in the first fraction of 4:1 MeOH/H_2O, while F-Ugi products **5** were collected in the second fraction of 100% MeOH. Nine F-Ugi products **5** from cyclohexylisocyanide **4**{***1***} and seven F-Ugi products **5** from methyl 2-isocyanoacetate **4**{***2***} were prepared. The average yield for **5** was 80%. The crude products were directly used for next step reaction without further purification.

The de-Boc/cyclizations were performed under microwave heating. The F-Ugi products **5** were dissolved in 10 equiv of 1:1 TFA/MeOH (v/v) and heated at 150 °C for 20 min under microwave irradiation. For most reactions, only target fluorous BZD (F-BZD) products **6** were obtained. However, for **6**{***3,2,1***} and **6**{***4,2,4***} two main spots were found by TLC analysis. The byproducts were confirmed to be the de-Boc but non-cyclized F-Ugi products by LC-MS analysis. In these cases, a second round of microwave reactions was performed to push the reaction to completion. Upon the completion of the cyclization reactions, 1 N aq. NaOH was added dropwise to neutralize the reaction mixtures. The crude products were purified by F-SPE and compounds **6** were collected in the second fraction of 100% MeOH. Sixteen F-BZD products **6** were obtained in 31−97% yields (Table 1). The average purity of the raw products checked by LC-MS at UV_{214nm} was 93%. All products were characterized by ^1H and ^{13}C NMR analysis (Supporting Information S6−S21).

Six boronic acids **7**{***1***−***6***} were used for Suzuki coupling reactions following the conditions reported in our previous paper (Scheme 5).[21,37] The reactions were carried out under microwave irradiation using 0.04 equiv of $Pd(dppf)Cl_2$ as a catalyst, 0.9 equiv of K_2CO_3 as a base, and 4:4:1 acetone/toluene/H_2O as a co-solvent. Thirty-one of thirty-three designed products **8** were obtained (Table 2). The final products were isolated by F-SPE and collected in the first fraction of 4:1 MeOH/H_2O or by flash chromatography. The structure and purity of all products were determined by LC-MS at UV_{214nm}, and the yield and purity were listed in Table 2. Representative compounds were further characterized by high resolution mass spectrometry, ^1H and ^{13}C NMR analysis (Supporting Information S21−S37).

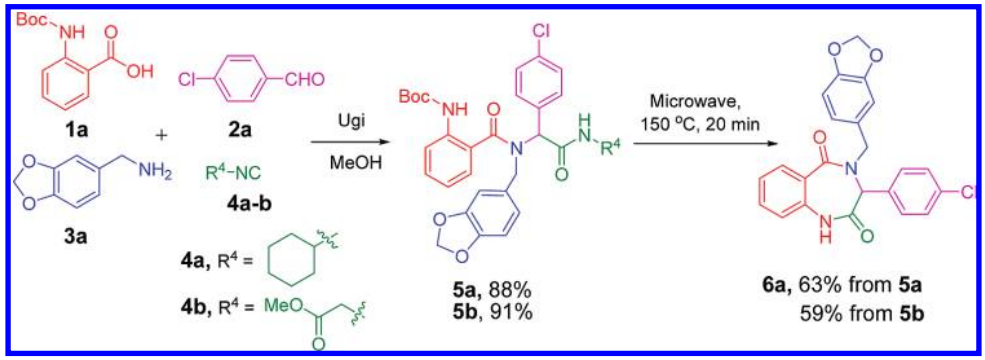
Conclusions

A new Ugi/de-Boc/cyclization/Suzuki strategy for the synthesis of biaryl-substituted 1,4-benzodiazepine-2,5-diones has been developed. Under microwave heating cyclohexylisocyanide and methyl 2-isocyanoacetate were used as convertible isocyanides for the cyclization reaction to form BZDs. The optimized solution-phase condition has been employed for fluorous parallel synthesis. Fluorous benzaldehyde was used as a tagged-component to simplify intermediates and final products purification by simple F-SPE. A four diversity points BZD library containing 31 members was synthesized to demonstrate the efficiency of library synthesis involving MCR, microwave heating, and fluorous separation.

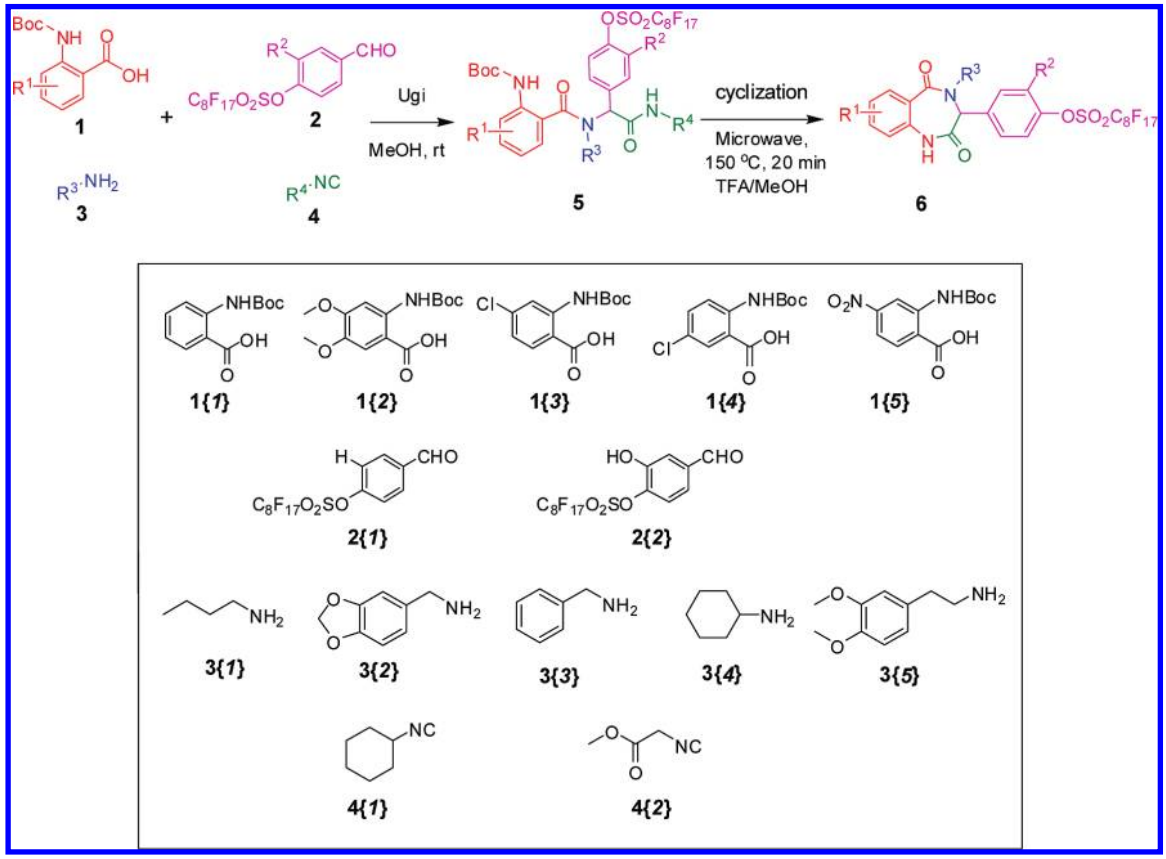
Experimental Section

The chemical reagents were purchased from Sigma-Aldrich (St. Louis, MO) and used without further purification. LC-MS were performed on a Waters system equipped with a Waters 2795 separation module, a Waters 2996 PDA detector, and a Micromass ZQ detector. A C_{18} column (2.0 μm, 2.0 × 50 mm) was used for the separation. The mobile

Scheme 3. Optimization of Microwave Synthesis of a BZD



Scheme 4. Microwave-Assisted Flourous Synthesis of BZDs



phases were methanol and water containing 0.05% trifluoroacetic acid. A linear gradient was used to increase from 10:90 v/v methanol/water to 100% methanol over 4.0 min and decrease to 10:90 v/v methanol/water over 6.5 min at a flow rate of 0.5 mL/min. The UV detection was at 214 nm. Mass spectra were recorded in positive ion mode using electrospray ionization (ESI). NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer using d-chloroform ($CDCl_3$) as solvent. Microwave assisted parallel synthesis was carried out on a Biotage Initiator single mode microwave reactor equipped with an automatic sample loader. GeneVac HT-12 Series II was used for the evaporation and concentration of samples after F-SPE. FluoroFlash SPE cartridges were purchased from Fluorous Technologies, Inc. (Pittsburgh, PA).

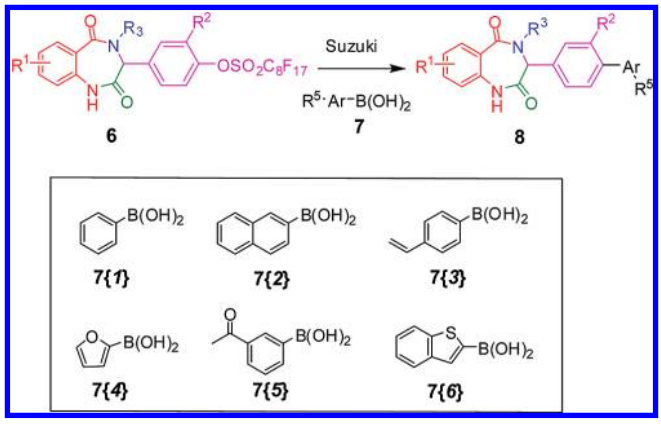
Synthesis of *tert*-Butyl 2-((benzo[*d*][1,3]dioxol-5-ylmethyl)(1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)carbamoyl)phenylcarbamate 5a. Piperonylamine (15 μL, 0.117 mmol) and 4-chlorobenzaldehyde (17 mg, 0.117 mmol) were dissolved in 1.0 mL of methanol. The mixture was stirred at room temperature for 1 h, and Boc-protected anthranilic acid (28 mg, 0.117 mmol) and 1-isocyanocyclohexane (15 μL, 0.117 mmol) were added in sequence. The resulting solution was stirred at room temperature overnight. After reaction completion, the reaction mixture was poured into a saturated sodium chloride solution and extracted twice with EtOAc. The organic layer was concentrated in vacuum, and the residue was purified by flash column chromatography on silica gel. A 64 mg portion of pure product was eluted with 1:3 hexane/EtOAc (yield 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.09 (d, J = 7.4, 1H), 7.49−7.12 (m, 6H), 6.99 (d, J = 6.4, 1H), 6.54 (d, J = 7.8, 1H), 6.27 (s, 2H), 6.00−5.81 (m, 2H), 5.73 (s, 1H), 5.45 (s, 1H), 4.50 (s, 1H), 4.26 (d, J = 15.8, 1H), 3.80 (dt, J = 14.6, 7.1, 1H), 1.89 (d, J = 9.4, 2H), 1.75−1.42 (m, 12H), 1.42−1.22 (m, 2H), 1.20−0.82 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.82, 168.25, 153.22, 147.63, 146.73, 136.31, 134.74,

Table 1. Characterization of the Representative Compounds **6**{R^1,R^2,R^3}

entry	compound	R^4	yield[a]	purity[b]	MW(found)[c]
1	**6**{*2*,*1*,*1*}	4{*1*}	31	95	867
2	**6**{*2*,*1*,*3*}	4{*1*}	36	98	901
3	**6**{*2*,*2*,*1*}	4{*1*}	44	98	897
4	**6**{*2*,*2*,*3*}	4{*1*}	48	96	931
5	**6**{*1*,*1*,*1*}	4{*1*}	64	98	807
6	**6**{*3*,*1*,*1*}	4{*1*}	87	97	841
7	**6**{*1*,*1*,*3*}	4{*1*}	76	98	841
8	**6**{*1*,*2*,*1*}	4{*1*}	79	>99	837
9	**6**{*3*,*2*,*1*}	4{*1*}	97	>99	871
10	**6**{*1*,*1*,*2*}	4{*2*}	62	94	885
11	**6**{*3*,*1*,*4*}	4{*2*}	52	83	867
12	**6**{*4*,*1*,*2*}	4{*2*}	60	92	919
13	**6**{*1*,*2*,*5*}	4{*2*}	65	90	945
14	**6**{*4*,*2*,*4*}	4{*2*}	77	69	897
15	**6**{*2*,*2*,*2*}	4{*2*}	64	94	975
16	**6**{*2*,*2*,*4*}	4{*2*}	64	82	923

[a] The yield (%) was calculated by the weight of the solid after F-SPE purification. [b] The purity (%) was based on the integration area of HPLC peaks detected at 214 nm. [c] MW (found) was determined by HPLC/ESI MS.

Scheme 5. Cleavage of Fluorous Tags by Suzuki Coupling Reactions under Microwave Irradiation



133.16, 131.29, 130.62, 128.83, 126.62, 124.74, 122.46, 120.54, 107.95, 107.54, 100.99, 80.31, 77.40, 77.29, 77.09, 76.77, 64.23, 52.73, 49.03, 32.65, 32.62, 28.36, 25.43, 24.79, 24.72.

Synthesis of Methyl 2-(2-(*N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(*tert*-butoxycarbonylamino)benzamido)-2-(4-chlorophenyl)acetamido)acetate 5b. Piperonylamine (15 μL, 0.117 mmol) and 4-chlorobenzaldehyde (17 mg, 0.117 mmol) were dissolved in 1.0 mL of methanol. The mixture was stirred at room temperature for 1 h, and Boc-protected anthranilic acid (28 mg, 0.117 mmol) and methyl 2-isocyanoacetate (11 μL, 0.117 mmol) were added in sequence. After reaction completion, the resulting solution was stirred at room temperature overnight. The reaction mixture was poured into a saturated sodium chloride solution and extracted twice with EtOAc. The organic layer was concentrated in vacuum, and the residue was purified by flash column chromatography on silica gel. 65 mg pure product was eluted with 1:1 hexane/EtOAc (yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44−7.90 (m, 2H), 7.55−7.15 (m, 6H), 7.00 (t, J = 6.8, 1H), 6.56 (d, J = 8.0, 1H), 6.33 (s, 3H), 5.87 (dd, J = 8.0, 1.3, 2H), 5.49 (s, 1H), 4.53 (s, 1H), 4.25 (d, J = 15.8, 1H), 4.14−3.90 (m, 2H), 3.74 (d, J = 12.0, 3H), 1.55 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.72, 169.90, 169.38, 158.15, 153.21, 147.71, 146.83, 136.19, 135.01, 132.54, 131.45, 130.67, 128.93, 126.64, 122.66, 120.58, 108.01, 107.58, 101.03, 80.42, 63.98, 52.40, 41.50, 28.36.

Table 2. Characterization of the Representative Compounds **8**{R^1,R^2,R^3,R^5}

entry	compound	yield[a]	purity[b]	MW(found)[c]
1	**8**{*2*,*1*,*1*,*1*}	56	96	445
2	**8**{*2*,*1*,*3*,*1*}	24	91	478
3	**8**{*2*,*2*,*1*,*2*}	20	97	525
4	**8**{*2*,*2*,*3*,*3*}	28	92	535
5	**8**{*2*,*2*,*3*,*6*}	27	93	565
6	**8**{*1*,*1*,*1*,*5*}	55	96	427
7	**8**{*1*,*1*,*1*,*2*}	31	93	435
8	**8**{*1*,*1*,*1*,*4*}	50	94	375
9	**8**{*3*,*1*,*1*,*1*}	67	95	419
10	**8**{*1*,*1*,*3*,*2*}	47	96	469
11	**8**{*1*,*1*,*3*,*3*}	35	89	445
12	**8**{*1*,*2*,*1*,*3*}	26	88	441
13	**8**{*1*,*2*,*1*,*5*}	42	91	457
14	**8**{*1*,*2*,*1*,*4*}	0	0	494
15	**8**{*3*,*2*,*1*,*5*}	39	98	491
16	**8**{*3*,*2*,*1*,*6*}	34	96	505
17	**8**{*1*,*1*,*2*,*1*}	59	87	463
18	**8**{*1*,*1*,*2*,*3*}	59	92	489
19	**8**{*1*,*1*,*2*,*4*}	40	96	453
20	**8**{*3*,*1*,*4*,*2*}	25	94	495
21	**8**{*3*,*1*,*4*,*4*}	44	95	435
22	**8**{*3*,*1*,*4*,*5*}	47	>99	487
23	**8**{*4*,*1*,*2*,*1*}	47	95	497
24	**8**{*4*,*1*,*2*,*6*}	26	95	553
25	**8**{*1*,*2*,*5*,*2*}	35	94	573
26	**8**{*1*,*2*,*5*,*3*}	38	82	549
27	**8**{*1*,*2*,*5*,*5*}	0	0	602
28	**8**{*4*,*2*,*4*,*6*}	22	94	532
29	**8**{*2*,*2*,*2*,*1*}	22	95	553
30	**8**{*2*,*2*,*2*,*4*}	20	90	543
31	**8**{*2*,*2*,*2*,*6*}	26	90	609
32	**8**{*2*,*2*,*4*,*2*}	21	91	551
33	**8**{*2*,*2*,*4*,*3*}	43	96	527

[a] The yield (%) was calculated by the weight of the solid after F-SPE purification. [b] The purity (%) was based on the integration area of HPLC peaks detected at 214 nm. [c] MW (found) was determined by HPLC/ESI MS.

Synthesis of 4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(4-chlorophenyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 6a. Compound 5a or 5b was dissolved in 400 μL of MeOH and 400 μL of TFA was added to the solution. The reaction took place in a monomode microwave cavity at 150 °C for 20 min. TLC was used to monitor the reaction process. After completing of reaction, two drops of 1N NaOH in water was added, and the mixture was extracted between saturated sodium chloride solution and EtOAc. The organic layer was dried under reduced pressure, and the residue was purified by flash column chromatography on silica gel, eluting with 1:2 hexane/EtOAc. The yields for reactions from 1-isocyanocyclohexane and methyl 2-isocyanoacetate were 63% and 59%, respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.67 (d, J = 7.8, 1H), 7.17 (dd, J = 12.1, 4.5, 1H), 6.96 (dd, J = 11.8, 8.0, 4H), 6.80 (dd, J = 21.7, 7.4, 3H), 6.67 (t, J = 7.9, 2H), 5.80 (d, J = 22.6, 2H), 5.28 (s, 1H), 4.86 (d, J = 14.0, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.30, 167.11, 148.20, 147.65, 134.00, 133.73, 132.58, 131.61, 131.16, 130.54, 129.74, 128.67, 127.26, 125.96, 125.23, 122.65, 119.93, 109.31, 108.41, 101.20.

General Procedure for the Synthesis of Compounds 5. Fluorous bezaldehydes **2** (0.4 mmol) and amines **3** (0.5 mmol) were dissolved in methanol and stirred for 1 h at

room temperature. Boc-protected anthranilic acids **1** (0.5 mmol) and isocyanides **4** (0.5 mmol) were added to the mixture in sequence. The reactions were stirred for further 10−24 h until the mixture became clear. TLC and HPLC/MS were used for monitoring the reaction. The reaction mixture was directly loaded on a Fluoro*Flash* SPE cartridge containing 10 g fluorous silica gel. The cartridge was eluted with 20 mL of MeOH/H_2O (v/v 4:1) following by 20 mL of MeOH. The second fraction was collected and concentrated to give compound **5** in various yields from 62% to 97%.

General Procedure for the Synthesis of Compounds 6. Compounds **5** were dissolved in 750 μL of MeOH, and 750 μL of TFA was added to the solution. The reaction took place in a monomode microwave cavity at 150 °C for 20 min. HPLC was used to monitor the reaction process. After completing of reaction, 1N NaOH in water was added dropwise for neutralization. The mixture was directly loaded on a Fluoro*Flash* SPE cartridge containing 10 g of fluorous silica gel. The cartridge was eluted with 20 mL of MeOH/H2O (v/v 4:1) following by 20 mL of MeOH. The second fraction was collected and concentrated to give compound **6.** The purity was checked by HPLC/MS/UV_{214nm}. Compounds **6** with lower purity were further purified by flash chromatography with silica gel using mixture of hexane and EtOAc as en eluent.

4-(4-Butyl-7,8-dimethoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*2,1,1*}. Yield 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.25−7.12 (m, 3H), 7.07 (d, J = 8.2, 2H), 6.12 (s, 1H), 5.33 (s, 1H), 4.07 (s, 1H), 3.78 (d, J = 11.5, 6H), 3.72−3.61 (m, 1H), 1.90−1.64 (m, 2H), 1.51−1.35 (m, 2H), 0.97 (dd, J = 14.9, 7.7, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.39, 166.41, 152.33, 148.99, 146.62, 134.55, 128.04, 126.34, 121.57, 120.03, 112.06, 102.57, 66.46, 56.12, 56.10, 51.10, 30.29, 20.07, 13.80; ESI-MS m/z 867(MH^+).

4-(4-Benzyl-7,8-dimethoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*2,1,3*}. Yield 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.49 (d, J = 5.2, 2H), 7.34 (t, J = 7.2, 2H), 7.31−7.23 (m, 1H), 7.18 (s, 1H), 6.97 (s, 4H), 6.13 (s, 1H), 5.38 (s, 1H), 5.11 (d, J = 14.2, 1H), 4.96 (d, J = 14.3, 1H), 3.78 (d, J = 19.9, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.25, 166.66, 152.51, 148.90, 146.62, 136.06, 134.24, 129.01, 128.39, 126.38, 121.38, 119.56, 112.13, 110.32, 102.67, 65.59, 60.44, 56.16, 56.12, 54.33, 21.08, 14.23; ESI-MS m/z 901(MH^+).

4-(4-Butyl-7,8-dimethoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*2,2,1*}. Yield 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.18 (s, 1H), 7.05−6.94 (m, 1H), 6.73 (s, 2H), 6.11 (s, 1H), 5.32 (s, 1H), 4.07 (dd, J = 16.1, 9.5, 1H), 3.78 (dd, J = 15.7, 10.9, 9H), 3.73−3.60 (m, 1H), 1.89−1.63 (m, 2H), 1.44 (dd, J = 14.7, 7.3, 2H), 1.07−0.89 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.26, 166.48, 152.37, 151.49, 146.69, 138.15, 135.48, 127.94, 122.44, 120.05, 117.08, 112.03, 109.57, 102.63, 66.72, 56.35, 56.15, 51.12, 30.30, 20.10, 13.80; ESI-MS m/z 897(MH^+).

4-(4-Benzyl-7,8-dimethoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*2,2,3*}. Yield 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.54 (t, J = 8.4, 2H), 7.34 (dt, J = 21.9, 7.1, 3H), 7.16 (s, 1H), 6.88 (d, J = 8.4, 1H), 6.56 (d, J = 7.3, 1H), 6.33 (s, 1H), 6.13 (s, 1H), 5.45−5.23 (m, 2H), 4.68 (d, J = 14.2, 1H), 3.77 (t, J = 12.1, 6H), 3.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.97, 166.63, 152.55, 151.37, 146.68, 138.04, 136.29, 129.39, 129.13, 128.46, 122.11, 119.59, 112.10, 109.80, 102.67, 65.91, 56.22, 56.18, 54.39; ESI-MS m/z 931(MH^+).

4-(4-Butyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*1,1,1*}. Yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.69 (d, J = 7.6, 1H), 7.20 (t, J = 11.7, 3H), 7.10−6.90 (m, 3H), 6.70 (d, J = 7.9, 1H), 5.36 (s, 1H), 4.13 (d, J = 12.2, 1H), 3.76−3.58 (m, 1H), 1.94−1.65 (m, 2H), 1.54−1.34 (m, 2H), 1.09−0.92 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.77, 166.67, 149.02, 134.24, 133.61, 132.29, 131.09, 127.95, 126.53, 125.29, 121.52, 119.83, 66.37, 51.11, 30.28, 20.09, 13.80; ESI-MS m/z 807(MH^+).

4-(4-Butyl-7-chloro-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*3,1,1*}. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.69 (s, 1H), 7.13 (dd, J = 18.2, 9.4, 5H), 6.67 (d, J = 8.4, 1H), 5.36 (s, 1H), 4.08 (s, 1H), 3.75−3.59 (m, 1H), 1.75 (dd, J = 20.5, 12.9, 2H), 1.44 (dd, J = 14.4, 7.1, 2H), 1.07−0.83 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.42, 165.38, 149.23, 133.91, 132.33, 132.20, 130.96, 130.69, 129.20, 126.47, 121.80, 121.31, 66.29, 51.27, 30.19, 20.07, 13.78; ESI-MS m/z 841(MH^+).

4-(4-Benzyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*]-[1,4]diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*1,1,3*}. Yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.73 (d, J = 7.5, 1H), 7.49 (d, J = 5.6, 2H), 7.34 (t, J = 6.9, 2H), 7.27 (dd, J = 7.8, 4.7, 1H), 7.20 (t, J = 7.1, 1H), 7.10−6.83 (m, 5H), 6.71 (d, J = 7.8, 1H), 5.40 (s, 1H), 5.14 (d, J = 14.3, 1H), 4.99 (d, J = 14.2, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.82, 167.00, 148.96, 135.98, 133.99, 132.48, 131.19, 129.12, 129.06, 128.45, 127.56, 126.60, 125.25, 121.35, 120.05, 65.58, 54.25; ESI-MS m/z 841(MH^+).

4-(4-Butyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*1,2,1*}. Yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.70 (d, J = 7.7, 1H), 7.22 (t, J = 7.4, 1H), 7.04 (t, J = 7.5, 1H), 6.97 (d, J = 8.6, 1H), 6.72 (d, J = 6.7, 3H), 5.35 (s, 1H), 4.10 (dd, J = 15.4, 8.3, 1H), 3.77 (d, J = 9.0, 3H), 3.73−3.62 (m, 1H), 1.45 (dd, J = 14.6, 7.3, 2H), 1.31−1.14 (m, 2H), 0.99 (t, J = 7.3, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.90, 166.87, 151.48, 138.16, 135.22, 133.71, 132.39, 131.00, 127.97, 125.37, 122.45, 119.96, 117.26, 109.70, 66.67, 60.48, 56.37, 51.14, 50.87, 30.30, 21.09, 20.13, 14.23, 13.81; ESI-MS m/z 837(MH^+).

4-(4-Butyl-7-chloro-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*3,2,1*}. Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.70 (s, 1H), 7.18 (d, J = 8.1, 1H), 7.03 (d, J = 8.1, 1H), 6.68 (d, J = 9.2, 3H), 5.35 (s, 1H),

4.05 (s, 1H), 3.80 (s, 3H), 3.73−3.61 (m, 1H), 1.95−1.55 (m, 2H), 1.44 (d, J = 6.7, 2H), 0.98 (t, J = 6.6, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.51, 165.56, 151.69, 138.39, 134.82, 132.42, 132.23, 131.02, 130.65, 129.25, 122.71, 121.43, 117.18, 109.64, 66.58, 56.42, 51.28, 50.90, 30.21, 20.10, 13.79; ESI-MS m/z 871(MH^+).

4-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*1*,*1*,*2*}. Yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.74 (d, J = 7.7, 1H), 7.23 (t, J = 7.5, 1H), 7.00 (ddd, J = 25.1, 16.6, 8.4, 7H), 6.79 (d, J = 7.8, 1H), 6.73 (d, J = 7.9, 1H), 5.94 (s, 1H), 5.90 (t, J = 4.6, 1H), 5.41 (s, 1H), 5.03 (d, J = 14.3, 1H), 4.93 (d, J = 14.2, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.40, 166.87, 148.93, 148.28, 147.76, 133.82, 132.49, 131.20, 129.70, 127.54, 126.58, 125.26, 122.72, 121.39, 119.85, 109.37, 108.51, 101.26; ESI-MS m/z 885(MH^+).

4-(7-Chloro-4-cyclohexyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*3*,*1*,*4*}. Yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.66 (t, J = 3.5, 1H), 7.22−7.15 (m, 2H), 7.12 (dd, J = 8.5, 2.5, 1H), 7.10−7.03 (m, 2H), 6.60 (d, J = 8.6, 1H), 5.47 (s, 1H), 4.96 (tt, J = 12.2, 3.5, 1H), 2.00 (d, J = 10.8, 1H), 1.89 (d, J = 10.7, 3H), 1.78−1.61 (m, 2H), 1.56−1.32 (m, 3H), 1.22−1.07 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.95, 165.29, 149.05, 134.58, 132.14, 132.01, 130.85, 130.77, 129.76, 126.58, 121.61, 121.14, 60.39, 55.63, 31.23, 30.09, 25.65, 25.44, 25.18; ESI-MS m/z 867(MH^+).

4-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-8-chloro-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)phenyl perfluorooctylsulfonate 6{*4*,*1*,*2*}. Yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.60 (d, J = 8.5, 1H), 6.92 (d, J = 14.2, 6H), 6.84 (d, J = 7.3, 1H), 6.75−6.62 (m, 2H), 5.85 (s, 1H), 5.82 (d, J = 1.1, 1H), 5.32 (s, 1H), 4.93 (d, J = 14.3, 1H), 4.81 (d, J = 14.4, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.41, 166.06, 149.12, 148.31, 147.84, 138.40, 134.89, 133.62, 132.64, 129.41, 126.51, 125.86, 125.53, 122.76, 121.61, 119.63, 109.31, 108.52, 101.29, 65.06, 53.96; ESI-MS m/z 919(MH^+).

4-(4-(3,4-Dimethoxyphenethyl)-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*1*,*2*,*5*}. Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.74 (d, J = 7.5, 1H), 7.25 (t, J = 7.5, 1H), 7.08 (t, J = 7.2, 1H), 7.04−6.93 (m, 1H), 6.84 (dd, J = 13.2, 8.6, 3H), 6.72 (d, J = 7.8, 3H), 5.44 (s, 1H), 4.31 (s, 1H), 4.04−3.92 (m, 1H), 3.89 (t, J = 9.9, 6H), 3.82−3.66 (m, 3H), 3.13 (s, 1H), 3.07−2.94 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.52, 166.83, 151.46, 149.01, 147.84, 138.18, 134.91, 133.60, 132.51, 130.99, 130.07, 127.72, 125.42, 122.43, 120.84, 119.96, 117.28, 111.99, 111.38, 109.73, 100.00, 66.89, 56.31, 55.91, 55.88, 52.75, 34.02; ESI-MS m/z 945(MH^+).

4-(8-Chloro-4-cyclohexyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*4*,*2*,*4*}. Yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.65 (d, J = 8.5, 1H), 7.01 (dd, J = 8.5, 2.0, 2H), 6.73 (dd, J = 7.9, 6.0, 3H), 5.48 (s, 1H), 4.98 (ddd, J = 12.0, 7.8, 3.6, 1H), 3.82 (d, J = 10.3, 3H), 2.01 (d, J = 11.3, 1H), 1.91 (d, J = 11.7, 3H), 1.82−1.67 (m, 2H), 1.50 (m, 3H), 1.26−1.10 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.32, 165.92, 151.51, 138.16, 138.02, 135.55, 134.53, 132.59, 126.78, 125.57, 122.48, 119.53, 117.30, 109.80, 60.61, 56.36, 55.61, 31.25, 30.21, 25.65, 25.46, 25.16; ESI-MS m/z 898(MH^+).

4-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-7,8-dimethoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*2*,*2*,*2*}. Yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.09 (s, 1H), 7.04 (s, 1H), 6.89 (d, J = 6.6, 1H), 6.83 (d, J = 8.4, 1H), 6.69 (d, J = 7.8, 1H), 6.50 (d, J = 7.6, 1H), 6.36 (s, 1H), 6.09 (s, 1H), 5.91−5.79 (m, 2H), 5.28 (s, 1H), 5.18 (d, J = 14.1, 1H), 4.51 (d, J = 14.3, 1H), 3.82−3.66 (m, 6H), 3.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.26, 166.62, 152.56, 151.39, 148.27, 147.72, 146.65, 138.01, 135.26, 130.06, 128.48, 122.86, 122.15, 119.52, 116.95, 112.04, 109.80, 109.56, 108.54, 102.71, 101.27, 65.60, 56.21, 56.16, 53.98, 35.62; ESI-MS m/z 975(MH^+).

4-(4-Cyclohexyl-7,8-dimethoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2-methoxyphenyl perfluorooctylsulfonate 6{*2*,*2*,*4*}. Yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.08 (s, 1H), 6.90 (d, J = 8.3, 1H), 6.66 (d, J = 10.2, 2H), 6.03 (s, 1H), 5.36 (s, 1H), 4.89 (dd, J = 16.3, 7.7, 1H), 3.83−3.56 (m, 9H), 1.91 (d, J = 10.7, 1H), 1.81 (d, J = 11.2, 3H), 1.71−1.52 (m, 2H), 1.37 (ddd, J = 20.0, 14.8, 7.9, 3H), 1.09 (t, J = 13.1, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.91, 166.36, 152.24, 151.32, 146.65, 137.96, 136.19, 127.76, 122.25, 120.65, 117.22, 112.19, 109.73, 102.48, 60.74, 56.33, 56.14, 56.11, 55.42, 31.29, 30.28, 25.72, 25.52, 25.24; ESI-MS m/z 923(MH^+).

General Procedure for the Synthesis of Compounds 8. To a reaction tube with a stirring bar was added compound **6** (0.033 mmol), **7** (0.028 mmol), Pd(pddf)Cl_2 (1.0 mg), and K_2CO_3 (9.0 mg, 0.066 mmol) in 900 μL of a 4:4:1 acetone/toluene/H_2O solvent. The reactions took place automatically in a monomode microwave cavity (150 °C, 20 min) of a Biotage Initiator single mode microwave reactor. HPLC was used to monitor the reaction. After reaction completion, the reaction mixture was washed with 0.8 mL of water, and the organic layer was loaded onto a 2 g Fluoro*Flash* SPE cartridge directly and washed with 4:1 MeOH/H_2O. The nonfluorous fractions were collected and concentrated. Finally, the fluorous fraction was eluted by MeOH for the reuse of cartridge.

3-(Biphenyl-4-yl)-4-butyl-7,8-dimethoxy-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*2*,*1*,*1*,*1*}. Yield 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 23.4, 1H), 7.40 (d, J = 7.5, 2H), 7.32 (t, J = 7.6, 4H), 7.25 (dd, J = 8.4, 6.1, 1H), 7.15 (s, 1H), 7.08 (d, J = 7.1, 2H), 6.05 (s, 1H), 5.31 (s, 1H), 4.04 (s, 1H), 3.71 (d, J = 14.9, 6H), 3.61 (ddd, J = 13.7, 7.3, 3.7, 1H), 1.71−1.54 (m, 2H), 1.37 (dd, J = 14.7, 7.4, 2H), 0.91 (t, J = 7.3, 3H); ESI-MS m/z 445(MH^+); HR-MS calcd for $C_{27}H_{29}N_2O_4$ $(M+H)^+$ 445.2127, found 445.2124.

4-Benzyl-3-(biphenyl-4-yl)-7,8-dimethoxy-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*2*,*1*,*3*,*1*}. Yield 24%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 3H), 7.35 (s, 2H), 7.30 (s, 5H), 7.23 (s, 4H), 6.92 (s, 2H), 6.03 (s, 1H), 5.36

(s, 1H), 4.97 (t, J = 13.5, 2H), 3.72 (d, J = 18.9, 6H); ESI-MS m/z 479(MH^+).

4-Butyl-7,8-dimethoxy-3-(3-methoxy-4-(naphthalen-2-yl)phenyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*2,2,1,2*}. Yield 20%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.72 (m, 3H), 7.54−7.37 (m, 5H), 7.19−7.05 (m, 2H), 6.76 (s, 1H), 6.66 (s, 1H), 6.08 (s, 1H), 5.36 (s, 1H), 4.04 (s, 1H), 3.82−3.72 (m, 6H), 3.66 (s, 4H), 1.70 (s, 2H), 1.42 (d, J = 7.8, 2H), 0.95 (t, J = 7.3, 3H); ESI-MS m/z 525(MH^+).

3-(4-(Benzo[b]thiophen-2-yl)-3-methoxyphenyl)-4-benzyl-7,8-dimethoxy-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*2,2,3,6*}. Yield 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.4, 1H), 7.64 (d, J = 7.2, 1H), 7.58−7.39 (m, 4H), 7.39−7.20 (m, 7H), 6.56 (s, 1H), 6.27 (s, 1H), 6.05 (s, 1H), 5.37 (s, 1H), 5.23 (d, J = 14.0, 1H), 4.69 (d, J = 14.7, 1H), 3.74 (d, J = 11.0, 6H), 3.56 (s, 3H); ESI-MS m/z 565(MH^+).

3-(3′-Acetylbiphenyl-4-yl)-4-butyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,1,5*}. Yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.89 (d, J = 7.1, 2H), 7.74 (s, 1H), 7.64 (d, J = 6.1, 1H), 7.50 (dd, J = 20.9, 13.3, 2H), 7.38 (s, 2H), 7.17 (s, 2H), 7.00 (s, 1H), 6.69 (s, 1H), 5.41 (s, 1H), 4.14 (s, 1H), 3.69 (s, 1H), 2.69−2.57 (m, 3H), 1.81 (s, 1H), 1.46 (d, J = 6.8, 2H), 1.35−1.12 (m, 1H), 1.08−0.75 (m, 3H); ESI-MS m/z 427(MH^+).

4-Butyl-3-(4-(naphthalen-2-yl)phenyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,1,2*}. Yield 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 46.1, 33.5, 4H), 7.67 (d, J = 9.6, 2H), 7.59−7.24 (m, 6H), 7.11 (s, 2H), 6.92 (s, 1H), 6.63 (d, J = 25.1, 1H), 5.36 (s, 1H), 4.08 (s, 1H), 3.67 (d, J = 30.9, 1H), 1.71 (s, 2H), 1.31 (d, J = 57.1, 2H), 1.03−0.71 (m, 3H); ESI-MS m/z 435(MH^+).

4-Butyl-3-(4-(furan-2-yl)phenyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,1,4*}. Yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.49 (m, 3H), 7.35 (d, J = 35.8, 3H), 7.01 (d, J = 32.6, 2H), 6.86 (s, 1H), 6.55 (s, 1H), 6.44 (s, 1H), 6.31 (s, 1H), 5.26 (s, 1H), 3.95 (d, J = 55.9, 1H), 3.56 (s, 1H), 1.33 (s, 3H), 1.14 (d, J = 14.6, 1H), 0.84 (t, J = 26.1, 3H); ESI-MS m/z 375(MH^+); HR-MS calcd for $C_{23}H_{23}N_2O_3$ $(M+H)^+$ 375.1709, found 375.1703.

4-Benzyl-3-(4-(naphthalen-2-yl)phenyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,3,2*}. Yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.65 (m, 6H), 7.55−7.42 (m, 3H), 7.40 (dd, J = 9.2, 5.6, 2H), 7.32 (d, J = 7.0, 3H), 7.18 (d, J = 4.3, 3H), 7.13 (s, 1H), 6.94 (s, 2H), 6.62 (d, J = 7.6, 1H), 5.41 (s, 1H), 5.18−4.85 (m, 2H); ESI-MS m/z 469(MH^+).

4-Benzyl-3-(4′-vinylbiphenyl-4-yl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,3,3*}. Yield 35%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.3, 1H), 7.64−7.57 (m, 1H), 7.44 (d, J = 7.5, 3H), 7.38−7.23 (m, 8H), 7.12 (t, J = 7.5, 1H), 7.00−6.83 (m, 3H), 6.69−6.53 (m, 2H), 5.68 (d, J = 17.6, 1H), 5.38 (s, 1H), 5.24−5.11 (m, 1H), 5.00 (t, J = 11.9, 2H); ESI-MS m/z 445(MH^+).

4-Butyl-3-(2-methoxy-4′-vinylbiphenyl-4-yl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,2,1,3*}. Yield 26%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.50 (s, 1H), 7.38−7.17 (m, 4H), 7.09 (s, 1H), 6.93 (d, J = 12.5, 2H), 6.68−6.41 (m, 4H), 5.63 (d, J = 17.8, 1H), 5.28 (s, 1H), 5.12 (d, J = 10.4, 1H), 4.00 (s, 1H), 3.56 (s, 4H), 1.64 (s, 2H), 1.35 (d, J = 7.1, 2H), 0.87 (d, J = 6.9, 3H); ESI-MS m/z 441(MH^+).

3-(3′-Acetyl-2-methoxybiphenyl-4-yl)-4-butyl-7-chloro-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*3,2,1,5*}. Yield 39%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 4.9, 1H), 7.84−7.78 (m, 1H), 7.69 (d, J = 3.7, 2H), 7.53 (d, J = 7.8, 1H), 7.47−7.35 (m, 2H), 7.12 (d, J = 6.6, 1H), 7.06 (d, J = 7.8, 1H), 6.68 (d, J = 6.7, 1H), 6.59 (d, J = 8.1, 1H), 5.34 (s, 1H), 4.03 (s, 1H), 3.74−3.51 (m, 4H), 2.62−2.46 (m, 3H), 1.81−1.62 (m, 2H), 1.38 (dt, J = 14.8, 7.5, 2H), 0.91 (dt, J = 11.0, 7.3, 3H); ESI-MS m/z 492(MH^+).

3-(4-(Benzo[b]thiophen-2-yl)-3-methoxyphenyl)-4-butyl-7-chloro-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*3,2,1,6*}. Yield 34%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 20.2, 7.9, 3H), 7.59 (d, J = 17.1, 2H), 7.43 (d, J = 8.3, 1H), 7.28−7.20 (m, 2H), 7.09 (d, J = 7.8, 1H), 6.67 (d, J = 6.8, 1H), 6.63−6.52 (m, 2H), 5.32 (s, 1H), 4.01 (s, 1H), 3.76 (d, J = 12.3, 3H), 3.72−3.53 (m, 1H), 1.69 (dd, J = 19.6, 11.7, 2H), 1.38 (dd, J = 14.9, 7.2, 2H), 0.92 (t, J = 7.3, 3H); ESI-MS m/z 505(MH^+); HR-MS calcd for $C_{28}H_{26}N_2O_3S$ $(M+H)^+$ 505.1353, found 505.1344.

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(biphenyl-4-yl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,2,1*}. Yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.79 (s, 1H), 7.54−7.35 (m, 4H), 7.30 (dd, J = 12.9, 7.2, 4H), 7.22 (d, J = 7.0, 1H), 7.02 (t, J = 22.7, 4H), 6.81 (d, J = 7.7, 1H), 6.72 (d, J = 7.1, 1H), 5.95 (t, J = 8.7, 2H), 5.47 (d, J = 6.9, 1H), 5.02 (d, J = 9.7, 2H); ESI-MS m/z 463(MH^+); HR-MS calcd for $C_{29}H_{23}N_2O_4$ $(M+H)^+$ 463.1658, found 463.1648.

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(4′-vinylbiphenyl-4-yl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,2,3*}. Yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.79 (d, J = 7.8, 1H), 7.46−7.37 (m, 4H), 7.31 (d, J = 8.3, 2H), 7.21 (t, J = 7.5, 1H), 7.07 (s, 1H), 7.05−6.93 (m, 4H), 6.84−6.67 (m, 3H), 6.01−5.92 (m, 2H), 5.78 (d, J = 17.6, 1H), 5.46 (s, 1H), 5.28 (d, J = 10.9, 1H), 5.09−4.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.16, 147.59, 139.94, 139.16, 136.90, 136.22, 132.31, 131.31, 130.01, 127.52, 126.89, 126.77, 126.62, 125.00, 122.61, 119.63, 114.16, 109.42, 108.43, 101.17; ESI-MS m/z 489(MH^+); HR-MS calcd for $C_{27}H_{29}N_2O_4$ $(M+H)^+$ 489.1814, found 489.1803.

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(4-(furan-2-yl)phenyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,1,2,4*}. Yield 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.75 (s, 1H), 7.42−7.29 (m, 3H), 7.29−7.21 (m, 2H), 7.18 (s, 1H), 7.09−6.84 (m, 4H), 6.78 (d, J = 8.1, 1H), 6.66 (s, 1H), 6.52 (d, J = 11.1, 1H), 6.41 (s, 1H), 5.88 (d, J = 54.9, 2H), 5.36 (d, J = 31.4, 1H), 4.98 (s, 2H); ESI-MS m/z 453(MH^+); HR-MS calcd for $C_{27}H_{29}N_2O_4$ $(M+H)^+$ 453.1450, found 453.1463.

7-Chloro-4-cyclohexyl-3-(4-(furan-2-yl)phenyl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*3,1,4,4*}. Yield 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 18.7, 2H), 7.62−7.37 (m, 4H), 7.14 (t, J = 19.1, 2H), 6.60 (s, 2H), 6.46 (s, 1H), 5.50 (s, 1H), 5.00 (s, 1H), 2.07 (s, 1H), 1.90 (s, 3H), 1.72 (s, 2H), 1.42 (d, J = 11.8, 2H), 1.32−1.05 (m,

2H); ESI-MS *m/z* 435(MH^+); HR-MS calcd for $C_{27}H_{29}N_2O_4$ $(M+H)^+$ 435.1475, found 435.1479.

3-(3′-Acetylbiphenyl-4-yl)-7-chloro-4-cyclohexyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*3,1,4,5*}. Yield 47%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.97 (s, 1H), 7.90 (d, $J = 7.6$, 1H), 7.66 (m, 2H), 7.50 (t, $J = 7.7$, 1H), 7.41 (d, $J = 8.3$, 2H), 7.25 (d, $J = 10.3$, 1H), 7.18 (d, $J = 8.0$, 2H), 7.11 (d, $J = 8.5$, 1H), 6.62 (d, $J = 8.6$, 1H), 5.52 (s, 1H), 5.00 (s, 1H), 2.72−2.52 (m, 3H), 2.05 (s, 1H), 1.89 (s, 3H), 1.72 (d, $J = 10.3$, 2H), 1.42 (d, $J = 9.7$, 2H), 1.29−1.04 (m, 2H); ESI-MS *m/z* 487(MH^+); HR-MS calcd for $C_{27}H_{29}N_2O_4$ $(M+H)^+$ 487.1788, found 487.1780.

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(biphenyl-4-yl)-8-chloro-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*4,1,2,1*}. Yield 47%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.64 (d, $J = 8.4$, 1H), 7.26 (ddd, $J = 43.1$, 28.5, 13.0, 8H), 6.92 (d, $J = 27.6$, 4H), 6.66 (dd, $J = 24.4$, 9.9, 2H), 5.85 (d, $J = 7.8$, 2H), 5.35 (d, $J = 12.6$, 1H), 5.02−4.71 (m, 2H); ESI-MS *m/z* 497(MH^+); HR-MS calcd for $C_{27}H_{29}N_2O_4$ $(M+H)^+$ 497.1268, found 497.1266.

3-(4-(Benzo[b]thiophen-2-yl)phenyl)-4-(benzo[*d*][1,3]-dioxol-5-ylmethyl)-8-chloro-3,4-dihydro-1*H*-benzo[*e*][1,4]-diazepine-2,5-dione 8{*4,1,2,6*}. Yield 26%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.57 (dd, $J = 25.4$, 6.9, 3H), 7.25 (d, $J = 8.7$, 3H), 7.10 (dd, $J = 23.3$, 10.1, 3H), 6.91−6.66 (m, 4H), 6.65−6.41 (m, 2H), 5.78 (d, $J = 7.3$, 2H), 5.25 (s, 1H), 4.78 (d, $J = 10.1$, 2H); ESI-MS *m/z* 553(MH^+).

4-(3,4-Dimethoxyphenethyl)-3-(2-methoxy-4′-vinylbiphenyl-4-yl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*1,2,5,3*}. Yield 38%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.41 (dd, $J = 29.0$, 16.7, 6H), 7.05 (d, $J = 35.3$, 2H), 6.87 (s, 3H), 6.81−6.55 (m, 3H), 5.87−5.68 (m, 1H), 5.53 (s, 1H), 5.28 (d, $J = 10.4$, 1H), 4.36 (s, 1H), 3.91 (d, $J = 9.8$, 7H), 3.68 (d, $J = 8.0$, 3H), 3.17 (s, 1H), 3.04 (s, 1H); ESI-MS *m/z* 549(MH^+); HR-MS calcd for $C_{27}H_{29}N_2O_4$ $(M+H)^+$ 549.2389, found 549.2371.

3-(4-(Benzo[b]thiophen-2-yl)-3-methoxyphenyl)-8-chloro-4-cyclohexyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*4,2,4,6*}. Yield 22%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.75−7.64 (m, 3H), 7.60 (s, 1H), 7.54−7.41 (m, 1H), 7.38−7.27 (m, 2H), 6.99 (d, $J = 6.1$, 1H), 6.75 (d, $J = 7.5$, 1H), 6.69 (d, $J = 10.8$, 2H), 5.50 (s, 1H), 4.98 (s, 1H), 3.84 (s, 3H), 2.05 (m, 1H), 1.88 (m, 3H), 1.69 (m, 2H), 1.40 (m, 2H), 1.21 (d, $J = 37.2$, 2H); ESI-MS *m/z* 532(MH^+).

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-7,8-dimethoxy-3-(2-methoxybiphenyl-4-yl)-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*2,2,2,1*}. Yield 22%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, $J = 35.5$, 2H), 7.43 (d, $J = 23.0$, 1H), 7.28 (d, $J = 5.6$, 4H), 7.06 (s, 1H), 6.93 (s, 2H), 6.72 (d, $J = 7.8$, 1H), 6.55 (s, 1H), 6.33 (s, 1H), 6.07 (s, 1H), 5.89 (d, $J = 5.5$, 2H), 5.36 (s, 1H), 5.15 (d, $J = 13.8$, 1H), 4.60 (d, $J = 14.4$, 1H), 3.75 (d, $J = 13.7$, 6H), 3.49 (s, 3H); ESI-MS *m/z* 553(MH^+).

3-(4-(Benzo[b]thiophen-2-yl)-3-methoxyphenyl)-4-(benzo-[*d*][1,3]dioxol-5-ylmethyl)-7,8-dimethoxy-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione 8{*2,2,2,6*}. Yield 26%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.62 (m, 3H), 7.59 (s, 2H), 7.34 (s, 2H), 7.09 (s, 2H), 6.92 (s, 1H), 6.73 (s, 1H), 6.58 (s, 1H), 6.37 (s, 1H), 6.08 (s, 1H), 5.90 (d, $J = 11.1$, 2H), 5.36 (d, $J = 10.6$, 1H), 5.19 (s, 1H), 4.57 (s, 1H), 3.74 (t, $J = 14.0$, 6H), 3.66 (d, $J = 10.7$, 3H); ESI-MS *m/z* 609(MH^+).

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Supporting Information Available. Respective ^1H, ^{13}C NMR and HRMS spectrum of compounds **6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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