Microwave-Assisted Fluorous Synthesis of a 1,4-Benzodiazepine-2,5-dione Library

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Fluorous displaceable linker-facilitated synthesis of 1,4-benzodiazepine-2,5-dione library has been developed. Perfluorooctanesulfonyl protected 4-hydroxy benzaldehydes were used as the limiting agent for Ugi four-component reactions to form condensed products. Postcondensation reactions of the Ugi products generated 1,4-benzodiazepine-2,5-dione ring skeleton. Microwave-assisted Suzuki coupling reactions removed the fluorous tag and introduced biaryl functionality to the benzodiazepine ring. The library scaffold has four points of substitution diversities. The fluorous tag facilitated the intermediate purifications using fluorous solid-phase extraction (F-SPE) and had no negative impact on the reactivity of the Ugi reactions and postcondensation reactions.

Introduction

1,4-Benzodiazepines have a broad range of biological utilities and have been employed as anxiolytic,[1] anticonvulsant,[2] antitumor,[3] and anti-HIV agents.[4] Among the family of benzodiazepines, 1,4-benzodiazepine-2,5-diones (BZDs) have been identified as inhibitors of platelet aggregation to mimic the arginine-glycine-aspartic acid (RGD) peptide sequence,[5] as precursors of benzodiazepines,[6,7] as anxiolytic agents,[8,9] and as Hdm2 antagonists to disrupt the p53-Hdm2 protein−protein interaction and induce cell growth arrest and apoptosis.[10−12] The development of new synthetic protocols for BZDs and preparation of BZD analog libraries for biological screening are topics of continuous interest. Over the years, syntheses of BDZs on solid-supported,[13−18] in ionic-liquid,[19] and conventional solution phase reactions[20,21] have been developed. When the BDZs were synthesized on solid-supported, high yields were obtained and the product separation was easier. However, the selection of linkers and the reaction condition optimization required significant amount of work. When BDZs were synthesized in ionic-liquid or solution phase, high yields were obtained, but the separation was always difficult. Introduced in this paper is a microwave-assisted fluorous approach for the synthesis of BDZs to accelerate intermediate separation and facilitate product synthesis.

In recent years, fluorous chemistry has gained increasing popularity in the synthesis of small molecule libraries.[22−24] Fluorous linkers are employed as the "phase tag" for fluorous solid-phase extraction (F-SPE).[25] The fluorous linker used in this project is perfluorooctanesulfonyl. It is different from the common protecting groups such as Boc, Cbz, Fmoc, and trityl, and has following functions in multistep library synthesis: (1) as a protection group for phenol,[26] (2) as a phase tag for F-SPE, and (3) as a triflate alternative for Pd-catalyzed reactions to introduce aryl, amine, thiol, and other functionalities to aryl and heteroaryl rings.[27]

Multicomponent reaction (MCR) such as Ugi four-component reaction is a powerful way to make library scaffolds containing a high number of substitution diversities.[28] Conducting post condensation reactions can lead to the generation of more complicated molecules. The advantage of using MCRs for construction of structurally diversified molecules can be enhanced through the incorporation of microwave and fluorous technologies.[29−31] Combinatorial techniques involving MCR, fluorous linker, and microwave heating have been applied for the synthesis of BDZ libraries. It was designed based on following three major transformations: (1) Ugi MCRs invloving benzaldehyde **2** as a fluorous component to form **5**, (2) cyclization of the Ugi products to form BDZs **6**, and (3) formation of **7** by microwave-assisted Suzuki reactions to cleave the F-linker and introduce the biaryl functionality to BDZs.

Results and Discussion

We developed two approaches for the synthesis of BDZs **6** using different benzoic acids **1** for the Ugi reactions. The first approach involving Boc-protected anthranilic acids **1**{*1*−*4*} is shown in Scheme 2. The fluorous benzaldehydes **2** were prepared by coupling of perfluorooctanesulfonyl fluoride with corresponding 4-hydroxybenzaldehydes. Two fluorous benzaldehydes **2**{*1*−*2*}, four Boc-protected anthranilic acids **1**{*1*−*4*}, five amino esters **3**{*1*−*5*}, and one cyclohexyl isocyanide **4** were used for Ugi reactions. As a demonstration of a feasible library synthesis, we did not carry out the full combination of the building blocks. Instead, we

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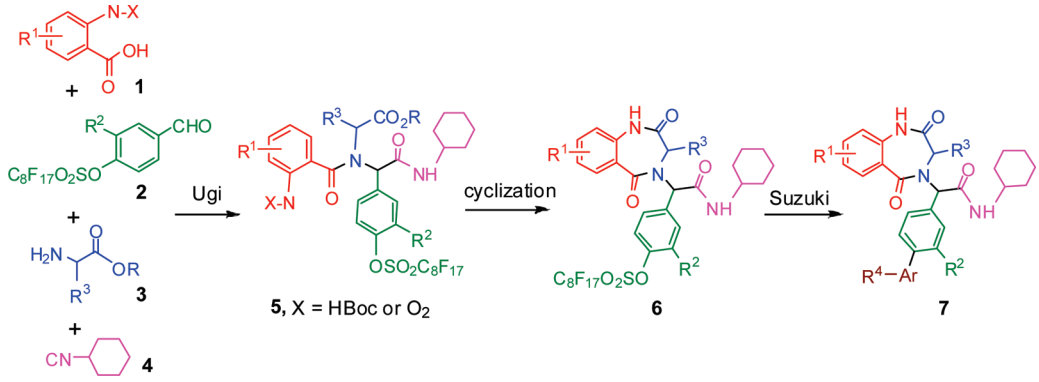
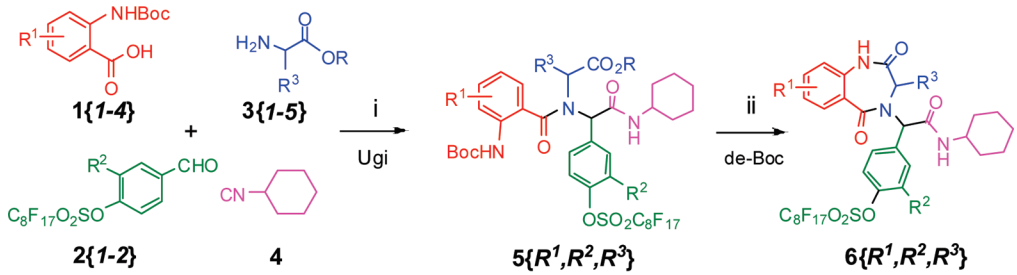
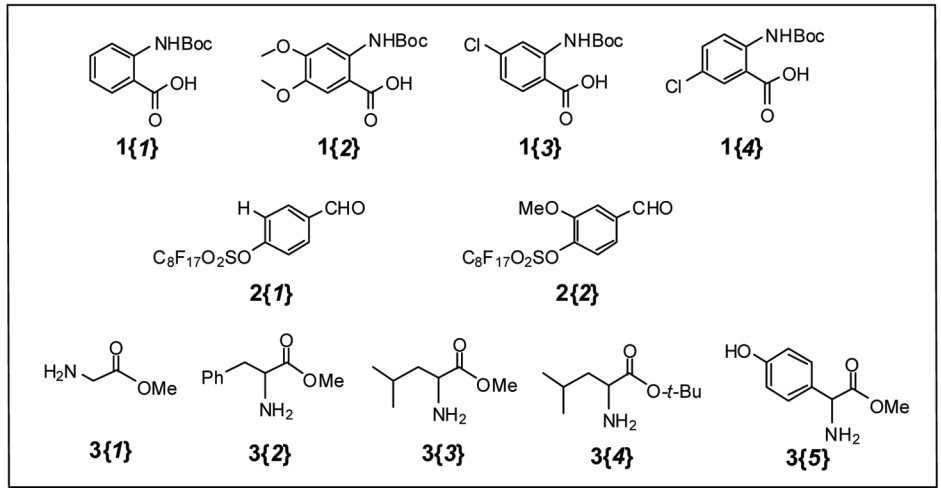
Scheme 1. General Transformations for the Preparation of a Biaryl-Substituted BDZ Library



Scheme 2. Boc-Anthranilic Acids **1**-Based Synthesis of F-BDZs **6**$\{R^1,R^2,R^3\}$[a]





[a] Reaction conditions: (i) KOH, MeOH, rt; (ii) AcCl, MeOH, 35 °C.

produced twenty-eight representative F-Ugi products **5**$\{R^1,R^2,R^3\}$. The F-Ugi products were then converted to the BDZs **6**$\{R^1,R^2,R^3\}$ by de-Boc/cyclizations (Scheme 2). In the nonfluorous synthesis of BDZs, equal molar amounts of four reaction components were used for the Ugi reactions.[20,32−34] In the fluorous synthesis, 2 equiv of the nonfluorous reactants **1**, **3**, and **4** were used to completely consume the fluorous component **2**. Reactions were promoted by KOH in MeOH at room temperature. The excess nonfluorous components were easily removed by F-SPE and twenty-eight F-Ugi products **5** were obtained with an average yield of 80% and an average purity of 86%. F-Ugi products **5** were isolated as a mixture of diastereomers, and no further attempt has been made to separate the diastereomers. All twenty-eight targeted products were obtained (Table 1). Twelve of twenty-eight products **5** were selected randomly for the de-Boc/cyclization reactions, which were performed using 10% acetyl chloride in methanol to afford twelve F-BDZs **6** after purification by F-SPE[35] (Table 2). The structures of ten F-BDZs **6** which were randomly selected and used in Suzuki reaction are listed in the top section of Scheme 4.

The second approach to synthesize F-BDZs **6** was using 2-nitrobenzoic acids **1**$\{5-7\}$ to replace anthranilic acids **1**$\{1-4\}$ for the Ugi reactions (Scheme 3). In this case, an optimized condition for Ugi reactions was **1/2/3/4** in a ratio of 2:1:2:1.6. Once the TLC showed the reaction was completed, the reaction mixture was purified by F-SPE to afford all eighteen F-Ugi products **5** in an average yield of 93% and an average purity of 97% as a mixture of diastereomers (Table 3). F-Ugi products **5** were then undergone zinc-promoted nitro reductions/cyclizations to yield eighteen F-BDZs **6** after F-SPE (Table 4). The structures of ten F-BDZs **6** which were randomly selected for Suzuki reaction are listed in the lower part of Scheme 4.

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

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**5**{*3*,*2*,*3*}	71%	85%	1142
2	**5**{*2*,*1*,*1*}	77%	93%	1082
3	**5**{*2*,*2*,*1*}	88%	89%	1112
4	**5**{*3*,*2*,*1*}	83%	97%	1086
5	**5**{*4*,*2*,*1*}	91%	97%	1086
6	**5**{*4*,*2*,*2*}	95%	59%	1176
7	**5**{*1*,*1*,*5*}	99%	74%	1114
8	**5**{*1*,*2*,*5*}	97%	96%	1144
9	**5**{*1*,*1*,*4*}	99%	90%	1120
10	**5**{*1*,*2*,*4*}	94%	94%	1150
11	**5**{*1*,*1*,*3*}	92%	92%	1078
12	**5**{*2*,*1*,*3*}	65%	54%	1138
13	**5**{*3*,*1*,*3*}	71%	90%	1112
14	**5**{*4*,*1*,*3*}	68%	96%	1112
15	**5**{*1*,*2*,*3*}	73%	85%	1108
16	**5**{*2*,*2*,*3*}	75%	85%	1168
17	**5**{*4*,*2*,*3*}	52%	85%	1142
18	**5**{*1*,*1*,*1*}	77%	93%	1022
19	**5**{*3*,*1*,*1*}	74%	93%	1056
20	**5**{*4*,*1*,*1*}	73%	89%	1056
21	**5**{*1*,*2*,*1*}	81%	90%	1052
22	**5**{*1*,*1*,*2*}	76%	86%	1112
23	**5**{*2*,*1*,*2*}	70%	76%	1172
24	**5**{*3*,*1*,*2*}	90%	90%	1146
25	**5**{*4*,*1*,*2*}	71%	57%	1146
26	**5**{*1*,*2*,*2*}	83%	98%	1142
27	**5**{*2*,*2*,*2*}	82%	98%	1202
28	**5**{*3*,*2*,*2*}	84%	67%	1176

[a] The yield (%) was calculated by the weight of the solid obtained after F-SPE. [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. Compounds in lines 11−28 were not used in the de-Boc/cyclization reactions.

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

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**6**{*1*,*1*,*5*}	76%	90%	982
2	**6**{*1*,*2*,*5*}	76%	90%	1012
3	**6**{*1*,*1*,*4*}	84%	93%	946
4	**6**{*1*,*2*,*4*}	84%	90%	976
5	**6**{*2*,*1*,*1*}	85%	98%	950
6	**6**{*2*,*2*,*1*}	79%	99%	980
7	**6**{*4*,*2*,*1*}	85%	91%	954
8	**6**{*3*,*2*,*1*}	83%	90%	954
9	**6**{*4*,*2*,*2*}	91%	99%	1044
10	**6**{*3*,*2*,*3*}	96%	95%	1010
11	**6**{*2*,*1*,*2*}	76%	94%	1040
12	**6**{*2*,*2*,*3*}	94%	94%	1036

[a] The yield (%) was calculated by the weight of the solid obtained after F-SPE. [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. Compounds in lines 11 and 12 were not used in the Suzuki coupling reactions.

One of the major advantages of F-sulfonyl linker is that it is displaceable and can be removed by Pd-catalyzed coupling reactions.[27] This "two birds with one stone" strategy combines the linker cleavage and introduction of another diversity group in a single operation. In this project, Suzuki reactions were used for F-linker cleavage and introduction of biaryl functionality to BDZs (Scheme 5). Eight boronic acids **8**{*1*−*8*} were selected for the coupling reactions. The Suzuki reactions were carried out under microwave heating using $Pd(dppf)Cl_2$ as a catalyst, K_2CO_3 as a base, and 4:4:1 acetone/toluene/water as a cosolvent.[27] We did not carry out all the reactions between the selected **6**s and eight boronic acids **8**. To demonstrate the general feasibility, we used randomly selected compounds **6** to react with compounds **8**{*1*−*8*}. The final products **7**{R^1,R^2,R^3,R^4} were isolated from the reaction mixtures by F-SPE. No reagent impurities were found from the final product by LC-MS and ^{1}H NMR analyses. However, Suzuki reactions between **6** and **8**{*8*} failed. Finally, thirty six final products **7** were produced, and their yields, purities (an average of UV_{TWC} and ELSD purities), and MS are displayed in Tables 5 and 6. All products existed as a mixture of diastereomers. The diastereomers and selected compounds were further characterized by HRMS and ^{1}H and ^{13}C NMR (Supporting Information).

Conclusions

Thirty-six 1,4-benzodiazepine-2,5-dione derivatives were synthesized by a combinatorial approach involving MCRs, fluorous linkers, and microwave heating. Ugi four-component reactions and sequential cyclizations quickly assemble the BDZ core bearing four diversity points. F-SPE simplified the intermediate purification process. Microwave-assisted Suzuki reactions cleaved the F-linker and introduced the biaryl group to the 1,4-benzodiazepine-2,5-dione core simultaneously.

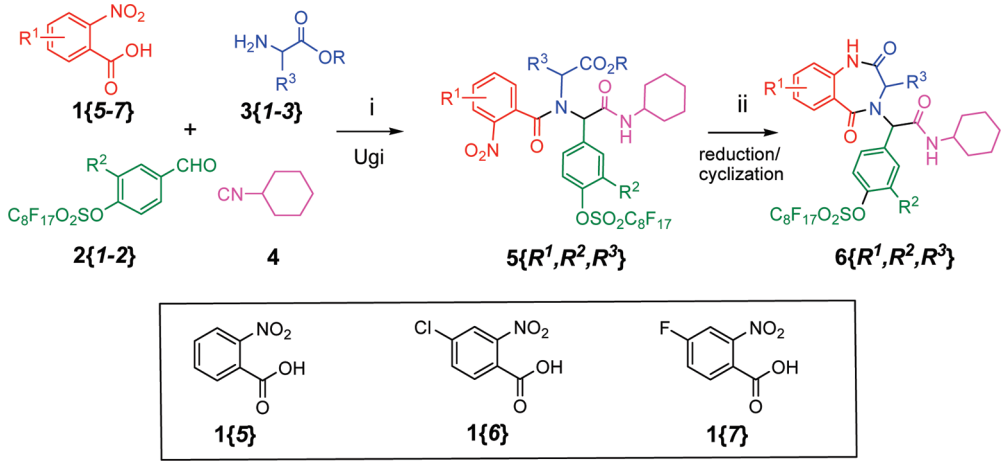
Experimental Section

The chemical reagents were purchased from Aldrich-Sigma (St.Luis, MO) and were used without further purification. LC-MS were performed on a Shimadzu system. A C_{18} column (2.0 μm, 2.0 × 50 mm) was used for the separation. The mobile phases were acetonitrile and water both containing 0.05% formic acid. A linear gradient was used to increase from 10:90 v/v acetonitrile/water to 100% acetonitrile over 8.0 min at a flow rate of 0.5 mL/min. The routine UV detection was at 214 nm and the purity of compounds was determined using an average of values from ELSD and UV_{TWC} detections.[36] Mass spectra were recorded in positive and negative ion mode using electrospray ionization. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer using d-chloroform as solvent.

General Procedure for F-SPE. A mixture containing fluorous and nonfluorous compounds in minimum amount of DMF was loaded onto a Fluor Flash@ cartridge preconditioned with 80:20 MeOH/H_2O. The cartridge was eluted with 80:20 MeOH/H_2O for the nonfluorous fraction, followed by the same amount of MeOH for the fluorous fraction. The vacuum was used to elute samples. The fluorous fraction was dried under reduced pressure. The cartridge was washed thoroughly with acetone/methanol, followed with 80:20 MeOH/H_2O, and reused.

General Procedure for Preparation of Compound 2 Shown in Scheme 2. To a magnetically stirred solution of 4-hydroxybenzaldehyde (or 4-hydroxy-3-methoxybenzaldehyde) (1.1 mmol) in DMF (5.0 mL) was added K_2CO_3 powder (1.2 mmol) at room temperature. The mixture was stirred for about 10 min before perfluorooctanesulfonyl fluoride (1.0 mmol) was added. The mixture was heated at 70 °C for 8 h until TLC showed the disappearance of starting materials. The cooled reaction mixture was filtered, and the solid was washed with EtOAc. The filtrate was extracted between EtOAc and water three times and the combined

Scheme 3. 2-Nitrobenzoic Acids **1**-Based Synthesis of F-BDZs **6**[a]



[a] Reaction conditions: (i) KOH, MeOH, rt; (ii) AcOH, MeOH, 35 °C.

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

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**5**{*6*,*1*,*3*}	84%	99%	1043
2	**5**{*5*,*2*,*3*}	95%	99%	1039
3	**5**{*7*,*2*,*3*}	90%	99%	1057
4	**5**{*5*,*1*,*1*}	78%	97%	952
5	**5**{*7*,*1*,*1*}	91%	99%	970
6	**5**{*5*,*2*,*1*}	95%	98%	982
7	**5**{*6*,*2*,*1*}	98%	97%	1017
8	**5**{*7*,*2*,*1*}	99%	97%	1000
9	**5**{*5*,*1*,*2*}	84%	99%	1042
10	**5**{*5*,*2*,*2*}	99%	98%	1072
11	**5**{*6*,*2*,*2*}	96%	96%	1107
12	**5**{*7*,*2*,*2*}	96%	92%	1090
13	**5**{*5*,*1*,*3*}	77%	96%	1008
14	**5**{*7*,*1*,*3*}	98%	99%	1027
15	**5**{*6*,*2*,*3*}	92%	89%	1072
16	**5**{*6*,*1*,*1*}	97%	98%	987
17	**5**{*6*,*1*,*2*}	100%	91%	1077
18	**5**{*7*,*1*,*2*}	96%	96%	1060

[a] The yield (%) was calculated by the weight of the solid obtained after F-SPE. [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. Compounds in lines 13−18 were not used in the nitro reductions/cyclizations.

Table 4. Characterization of the Representative Compounds **6**{R^1,R^2,R^3} of Scheme 3

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**6**{*6*,*1*,*3*}	83%	69%	980
2	**6**{*5*,*2*,*3*}	91%	89%	976
3	**6**{*7*,*2*,*3*}	89%	83%	994
4	**6**{*5*,*1*,*1*}	76%	92%	890
5	**6**{*7*,*1*,*1*}	91%	82%	908
6	**6**{*5*,*2*,*1*}	84%	67%	920
7	**6**{*6*,*2*,*1*}	53%	67%	954
8	**6**{*7*,*2*,*1*}	66%	68%	938
9	**6**{*5*,*1*,*2*}	74%	28%	980
10	**6**{*5*,*2*,*2*}	86%	98%	1010
11	**6**{*6*,*2*,*2*}	95%	93%	1044
12	**6**{*7*,*2*,*2*}	93%	62%	1028
13	**6**{*5*,*1*,*3*}	91%	88%	946
14	**6**{*7*,*1*,*3*}	79%	87%	964
15	**6**{*6*,*2*,*3*}	78%	84%	1010
16	**6**{*6*,*1*,*1*}	84%	82%	924
17	**6**{*6*,*1*,*2*}	86%	92%	1014
18	**6**{*7*,*1*,*2*}	91%	83%	998

[a] The yield (%) was calculated by the weight of the solid obtained after F-SPE. [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. Compounds in lines 13−18 were not used in the Suzuki coupling reactions.

organic phase was washed with brine and dried over anhydrous Na_2SO_4 overnight. After concentrated under reduced pressure, the crude product was purified by F-SPE as described above.

General Procedure for Preparation of Compounds 1{*1*−*4*}. To a magnetically stirred solution of anthranilic acid (1.0 mmol) in acetone (5.0 mL) was added NaOH powder (2.0 mmol) at room temperature and then di-*tert*-butyl dicarbonate (3.0 mmol) was added. The mixture was stirred at room temperature for 5 h until TLC showed the disappearance of anthranilic acid. The reaction mixture was added 2 mL water and distilled under reduced pressure to remove the acetone. The residue was washed with petroleum ether three times. The aqueous phase was added HCl (1 N) until the pH was less than 2. The mixture was extracted between EtOAc and water three times and the combined organic phase was washed by HCl (1 N), water and brine in turn. The organic phase was dried by anhydrous Na_2SO_4 overnight and distilled under reduced pressure to obtain compounds **1**{*1*−*4*}.

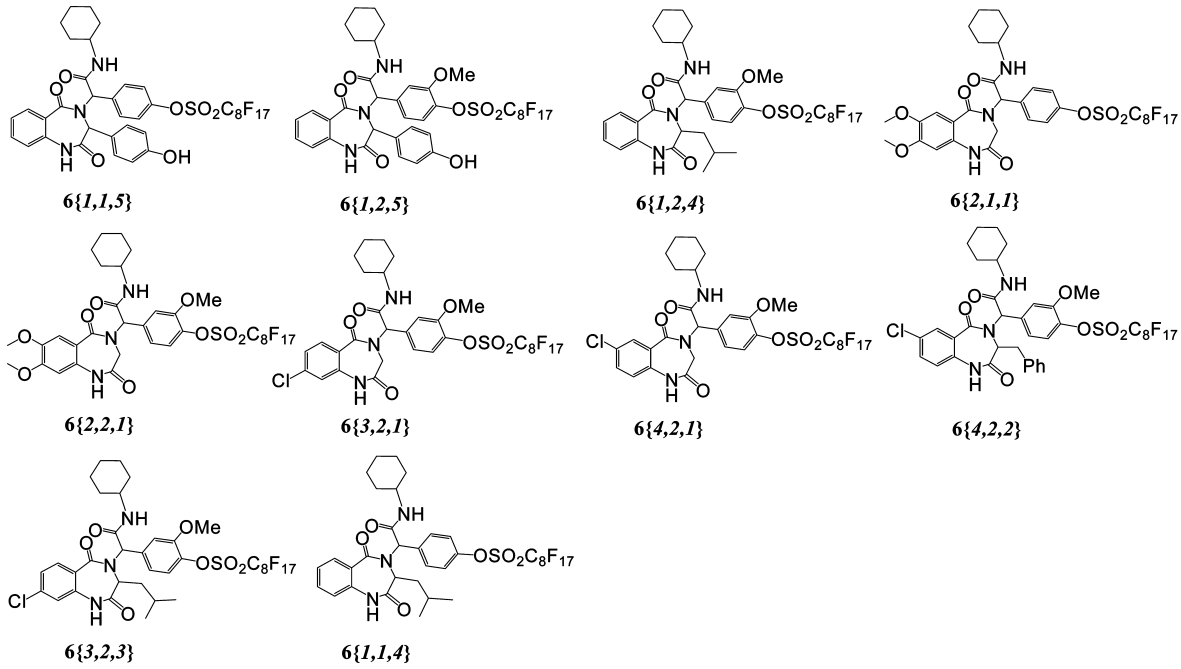
General Procedure for Preparation of Compound 5 of Scheme 2. The potassium hydroxide (2.0 equiv) and fluorous benzaldehydes **2** (1.0 equiv) were dissolved in methanol to a concentration of 1 M, then the glycine methyl ester hydrochloride **3** (2.0 equiv) was added. This solution was allowed to stand for 1 h, and then the di-*tert*-butyl protected anthranilic acid **1**{*1*−*4*} (2.0 equiv) was added, followed by the addition of cyclohexyl isocyanide **4** (2.0 equiv). The resulting solution was shaken on a parallel reactor bed at room temperature for 24 h. When TLC showed the reaction was completed, the reaction mixture was purified by F-SPE using a standard procedure.

General Procedure for Preparation of Compound 6. The compounds **5** were dissolved in a 10% solution of acetyl chloride (AcCl) in MeOH to a concentration of 1 M. The solution was shaken on a parallel reactor at 35 °C for 12 h. When TLC showed the reaction was completed, the reaction mixture was purified by F-SPE.

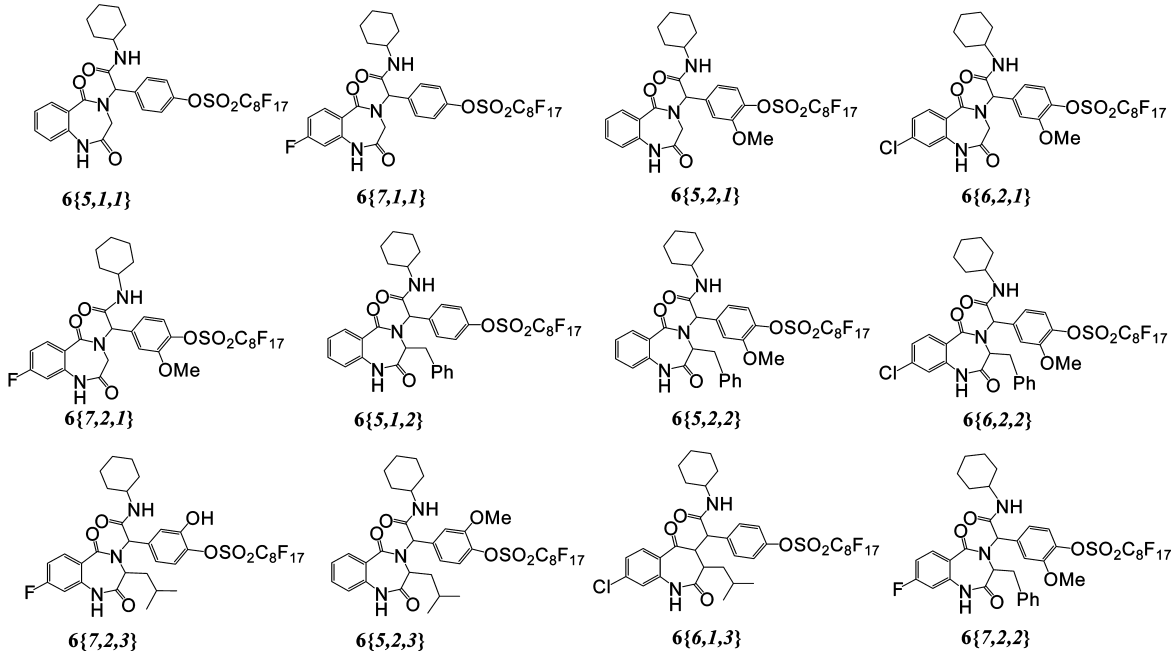
4-(2-(Cyclohexylamino)-1-(3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-oxoethyl)phenyl Per-

Scheme 4. Structures of Twenty-Two F-BDZs **6**{R^1,R^2,R^3}

Prepared by Boc-Anthranilic Acids **1**-Based Synthesis (Scheme 2)



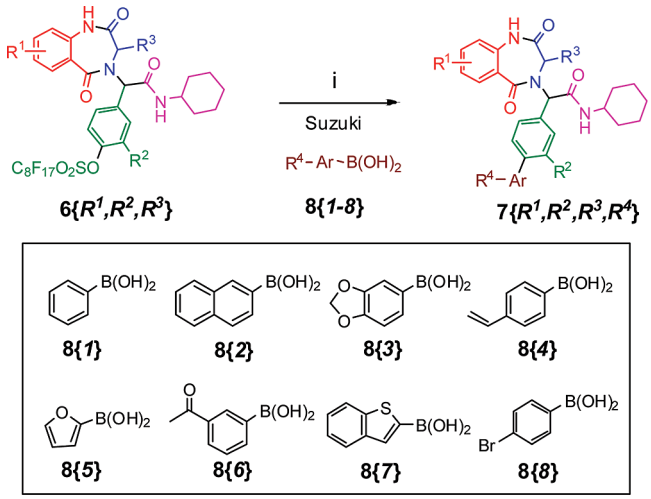
Prepared by 2-Nitrobenzoic Acids **1**-Based Synthesis (Scheme 3)



fluorooctylsulfonate 6{*1,1,4*}: yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 21.6, 1H), 7.91 (dd, J = 18.3, 8.0, 1H), 7.58 (d, J = 8.7, 1H), 7.52−7.33 (m, 3H), 7.32−6.95 (m, 5H), 6.84 (d, J = 8.0, 1H), 6.47 (d, J = 132.6, 1H), 5.90 (dd, J = 137.0, 8.0, 1H), 4.14 (dd, J = 21.9, 8.7, 1H), 3.78 (s, 2H), 1.87 (s, 3H), 1.60 (dd, J = 39.1, 13.0, 5H), 1.43−0.90 (m, 11H), 0.89−0.72 (m, 3H), 0.72−0.49 (m, 3H), 0.39 (dd, J = 22.7, 15.5, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.73, 171.68, 167.22, 167.07, 149.68, 135.03, 133.20, 131.25, 125.80, 124.78, 122.06, 121.94, 119.74, 61.92, 59.27, 59.22, 48.91, 48.70, 41.24, 39.30, 38.16, 32.90, 32.75, 25.85, 25.44, 25.08, 24.75, 24.70, 23.05, 21.40, 21.03; ESI-MS m/z 946 (MH^+).

4-(2-(Cyclohexylamino)-1-(3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-oxoethyl)-2-methoxyphenyl Perfluorooctylsulfonate 6{*1,2,4*}: yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−7.85 (m, 3H), 7.54−7.28 (m, 2H), 7.26−7.04 (m, 5H), 7.03−6.88 (m, 1H), 6.87−6.73 (m, 2H), 6.58 (s, 0H), 6.26 (s, 1H), 5.96 (d, J = 8.0, 1H), 5.63 (s, 0H), 4.19 (dd, J = 15.9, 11.5, 2H), 3.95−3.67 (m, 7H), 1.87 (s, 4H), 1.60 (dd, J = 37.3, 13.2, 10H), 1.44−0.93 (m, 13H), 0.84 (dd, J = 6.5, 3.7, 1H), 0.77 (d, J = 6.3, 3H),

Scheme 5. Fluorous Linker Cleavage by Suzuki Coupling Reactions[a]



[a] Reaction conditions: (i) Pd(pddf)Cl_2, K_2CO_3, acetone/toluene/H_2O(4:4:1), MW. 150 °C.

Table 5. Characterization of the Representative Compounds **7**{R^1,R^2,R^3,R^4} (Scheme 2)

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**7**{*2,2,1,1*}	10%	>90%	558 (MH^+)
2	**7**{*4,2,1,1*}	26%	>90%	532 (MH^+)
3	**7**{*1,2,4,1*}	17%	>90%	554 (MH^+)
4	**7**{*3,2,1,1*}	21%	>90%	532 (MH^+)
5	**7**{*3,2,4,1*}	15%	98%	588 (MH^+)
6	**7**{*1,1,4,5*}	10%	87%	514 (MH^+)
7	**7**{*1,1,4,6*}	76%	93%	566 (MH^+)
8	**7**{*2,1,1,7*}	36%	100%	584 (MH^+)
9	**7**{*2,1,1,2*}	42%	100%	578 (MH^+)
10	**7**{*2,2,1,3*}	53%	97%	602 (MH^+)
11	**7**{*3,2,1,4*}	19%	89%	558 (MH^+)
12	**7**{*4,2,1,5*}	17%	90%	522 (MH^+)
13	**7**{*4,2,1,6*}	35%	91%	574 (MH^+)
14	**7**{*4,2,2,2*}	23%	98%	672 (MH^+)
15	**7**{*3,2,4,7*}	21%	100%	644 (MH^+)
16	**7**{*1,1,5,6*}	49%	99%	602 (MH^+)
17	**7**{*1,1,5,7*}	54%	99%	616 (MH^+)
18	**7**{*1,2,5,3*}	15%	86%	634 (MH^+)
19	**7**{*1,2,5,4*}	12%	89%	616 (MH^+)
20	**7**{*4,2,2,8*}	0%		
21	**7**{*1,2,4,8*}	0%		

[a] The yield (%) was calculated by the weight of the solid obtained after F-SPE. [b] The purity (%) was an average of UV_{TWC} and ELSD purities. [c] MW (found) was determined by HPLC/ESI MS. Compounds in lines 20 and 21 were not obtained.

0.61 (d, J = 6.4, 3H), 0.39 (d, J = 6.6, 2H);^{13}C NMR (101 MHz, $CDCl_3$) δ 171.76, 167.22, 167.10, 151.79, 138.96, 135.96, 134.96, 133.21, 132.01, 131.76, 125.85, 124.81, 122.73, 121.76, 119.61, 114.19, 62.36, 59.27, 56.57, 56.35, 48.91, 48.73, 39.37, 38.23, 32.91, 32.73, 25.82, 25.43, 25.11, 24.71, 23.08, 22.68, 22.47, 21.38, 21.10; ESI-MS m/z 976 (MH^+).

4-(2-(Cyclohexylamino)-1-(7,8-dimethoxy-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-oxoethyl)phenyl Perfluorooctylsulfonate 6{*2,1,1*}: yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.45 (d, J = 8.5, 2H), 7.35 (s, 1H), 7.32−7.10 (m, 3H), 6.30 (d, J = 19.3, 2H), 5.78 (d, J = 7.7, 1H), 4.19−3.54 (m, 9H), 1.88 (s, 2H), 1.61 (s, 8H), 1.27 (s, 2H), 1.20−0.87 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.99, 167.88, 167.31, 152.96, 149.78, 146.45, 135.12, 131.38, 130.69, 122.13, 116.92, 113.17, 103.33, 89.89, 61.04, 56.33, 56.28, 49.01, 47.97, 32.92, 32.79, 25.39, 24.82, 24.74; ESI-MS m/z 950 (MH^+).

Table 6. Characterization of the Representative Compounds **7**{R^1,R^2,R^3,R^4} (Scheme 3)

entry	compound	yield[a]	purity[b]	MW (found)[c]
1	**7**{*5,1,2,1*}	23%	>90%	558 (MH^+)
2	**7**{*5,2,2,1*}	20%	>90%	588 (MH^+)
3	**7**{*6,2,2,1*}	15%	>90%	622 (MH^+)
4	**7**{*7,2,2,1*}	18%	>90%	606 (MH^+)
5	**7**{*5,1,1,1*}	25%	>90%	468 (MH^+)
6	**7**{*6,1,3,2*}	38%	95%	608 (MH^+)
7	**7**{*6,1,3,6*}	28%	91%	600 (MH^+)
8	**7**{*5,2,3,3*}	24%	94%	598 (MH^+)
9	**7**{*7,2,3,4*}	19%	96%	598 (MH^+)
10	**7**{*7,2,3,7*}	47%	94%	628 (MH^+)
11	**7**{*7,1,1,2*}	50%	99%	536 (MH^+)
12	**7**{*7,1,1,5*}	24%	96%	476 (MH^+)
13	**7**{*5,2,1,3*}	47%	99%	542 (MH^+)
14	**7**{*5,2,1,6*}	44%	17%	540 (MH^+)
15	**7**{*6,2,1,4*}	49%	87%	558 (MH^+)
16	**7**{*7,2,1,5*}	47%	99%	506 (MH^+)
17	**7**{*7,2,1,7*}	32%	99%	572 (MH^+)
18	**7**{*5,2,3,8*}	0%		
19	**7**{*5,1,1,2*}	0%		

[a] The yield (%) was calculated by the weight of the solid obtained after F-SPE. [b] The purity (%) was an average of UV_{TWC} and ELSD purities. [c] MW (found) was determined by HPLC/ESI MS. Compounds in lines 18 and 19 were not obtained.

4-(2-(Cyclohexylamino)-1-(7,8-dimethoxy-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-oxoethyl)-2-methoxyphenyl Perfluorooctylsulfonate 6{*2,2,1*}: yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.35 (s, 1H), 7.24−7.09 (m, 1H), 7.05 (s, 1H), 6.96 (d, J = 8.4, 1H), 6.33 (s, 1H), 6.23 (s, 1H), 5.78 (d, J = 8.0, 1H), 4.02−3.66 (m, 13H), 1.87 (s, 2H), 1.59 (d, J = 12.4, 7H), 1.22 (d, J = 32.2, 3H), 1.14−0.98 (m, 3H); ESI-MS m/z 980 (MH^+).

4-(1-(8-Chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(cyclohexylamino)-2-oxoethyl)-2-methoxyphenyl Perfluorooctylsulfonate 6{*3,2,1*}: yield 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−7.71 (m, 2H), 7.49−6.74 (m, 8H), 6.23 (s, 1H), 5.64 (s, 1H), 4.23−3.16 (m, 9H), 1.98 (d, J = 95.9, 3H), 1.55 (s, 8H), 1.35−0.86 (m, 8H); ESI-MS m/z 955 (MH^+).

4-(1-(7-Chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(cyclohexylamino)-2-oxoethyl)-2-methoxyphenyl Perfluorooctylsulfonate 6{*4,2,1*}: yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.90 (d, J = 2.4, 1H), 7.37 (dd, J = 8.5, 2.4, 1H), 7.18 (d, J = 8.2, 1H), 7.05 (s, 1H), 6.97 (d, J = 8.4, 1H), 6.83 (d, J = 8.6, 1H), 6.24 (s, 1H), 5.69 (d, J = 8.0, 1H), 3.97−3.62 (m, 7H), 1.87 (s, 2H), 1.75−1.46 (m, 6H), 1.37−1.16 (m, 3H), 1.15−0.93 (m, 4H);^{13}C NMR (101 MHz, $CDCl_3$) δ 170.12, 166.99, 166.88, 152.01, 139.20, 135.58, 134.66, 133.14, 131.83, 130.71, 126.40, 122.97, 122.05, 121.85, 114.38, 61.44, 56.47, 49.07, 47.52, 32.92, 32.76, 25.36, 24.80, 24.74; ESI-MS m/z 955 (MH^+).

4-(1-(3-Benzyl-7-chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(cyclohexylamino)-2-oxoethyl)-2-methoxyphenyl perfluorooctylsulfonate 6{*4,2,2*}: yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.89 (s, 1H), 7.21 (d, J = 7.5, 1H), 7.14−6.94 (m, 5H), 6.92−6.63 (m, 4H), 6.43−6.12 (m, 3H), 5.73 (t, J = 112.7, 1H), 4.46−4.10 (m, 1H), 3.69 (d, J = 31.1, 5H), 3.15 (d, J =

9.8, 1H), 2.47 (t, J = 13.0, 1H), 2.01 (dd, J = 62.3, 40.5, 2H), 1.58 (t, J = 40.0, 5H), 1.26 (s, 2H), 1.17−0.98 (m, 4H), 0.93 (s, 1H);^{13}C NMR (101 MHz, $CDCl_3$) δ 171.12, 167.05, 165.85, 151.83, 138.95, 135.86, 135.67, 133.95, 133.75, 133.37, 131.55, 131.18, 130.42, 129.01, 128.77, 128.66, 127.24, 126.97, 122.83, 121.93, 121.30, 113.71, 62.34, 62.09, 56.29, 48.95, 38.13, 35.55, 32.92, 32.74, 25.40, 24.76; ESI-MS m/z 1044 (MH^+).

4-(1-(8-Chloro-3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(cyclohexylamino)-2-oxoethyl)-2-methoxyphenyl Perfluorooctylsulfonate 6{*3,2,3*}: yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 52.1, 1H), 7.86 (dd, J = 15.6, 8.5, 1H), 7.27−6.69 (m, 7H), 6.36 (d, J = 149.6, 1H), 5.87 (t, J = 90.2, 1H), 4.19 (d, J = 11.1, 1H), 3.98−3.54 (m, 7H), 2.85 (d, J = 30.1, 1H), 1.88 (s, 2H), 1.73−1.46 (m, 7H), 1.44−0.91 (m, 9H), 0.90−0.72 (m, 3H), 0.64 (d, J = 6.3, 3H), 0.40 (dd, J = 6.5, 3.0, 2H);^{13}C NMR (101 MHz, $CDCl_3$) δ 171.70, 167.14, 166.47, 151.87, 139.05, 137.33, 136.11, 135.75, 133.46, 125.03, 124.19, 122.85, 121.77, 119.51, 114.11, 62.79, 59.11, 56.34, 48.79, 46.14, 38.27, 37.79, 32.86, 32.79, 32.72, 31.64, 25.90, 25.41, 25.34, 25.17, 24.76, 24.70, 23.08, 22.68, 21.30, 21.05; ESI-MS m/z 1010 (MH^+).

General Procedure for Preparation of Compound 5 Following Scheme 3. The potassium hydroxide (2.0 equiv) and 2-Nitrobenzoic acid **1**{*5*−*7*} (2.0 equiv) were dissolved in methanol to a concentration of 2 M. The solution was allowed to stand for 1 h. Then the L-phenylalanine methyl ester hydrochloride **3**{*1*−*3*} (2.0 equiv), cyclohexyl isocyanide **4** (1.6 equiv) and fluorous benzaldehydes **2** (1.0 equiv) were added, the solution was shaken on a parallel reactor at room temperature for 24 h. When TLC showed the reaction was completed, the reaction mixture was purified by F-SPE.

General Procedure for Preparation of Compound 6. The compounds **5** (1.0 equiv) were dissolved in a 50% solution of acetic acid (AcOH) in MeOH to an approximate concentration of 1 M in each and were treated with zinc powder (25 equiv). The solution were shaken on a parallel reactor at 35 °C for 12 h. When TLC showed the reaction was completed, the reaction mixture was filtrated to remove the unreacted zinc powder. The filtrate was distilled under reduced pressure and purified by F-SPE.

4-(2-(Cyclohexylamino)-1-(2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-oxoethyl)phenyl Perfluorooctylsulfonate 6{*5,1,1*}: yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.92 (d, J = 7.8, 1H), 7.44 (dd, J = 22.1, 7.8, 3H), 7.22 (dd, J = 18.4, 6.9, 4H), 6.87 (d, J = 7.8, 1H), 6.34 (s, 1H), 5.82 (d, J = 7.8, 1H), 4.03−3.66 (m, 4H), 1.87 (s, 2H), 1.58 (dd, J = 35.0, 12.7, 5H), 1.36−1.15 (m, 4H), 1.15−0.90 (m, 4H); ESI-MS m/z 890 (MH^+).

General Procedure for Preparation of Compounds 7. To a reaction tube with a stirring bar was added compound **7** (1.0 mmol), **8** (0.9 mmol), Pd(pddf)Cl_2 (0.04 mmol), and K_2CO_3 (2.0 mmol) in 0.6 mL 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 the reaction, the reaction mixture was washed with 0.8 mL of water, and the organic layer was loaded onto a 2 g FluoroFlash cartridge directly and washed with 80:20 MeOH/H_2O. The nonfluorous fractions were collected and concentrated. Finally, the fluorous fraction was eluted by methanol for the reuse of cartridge.

***N*-Cyclohexyl-2-(7,8-dimethoxy-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(2-methoxybiphenyl-4-yl)acetamide 7{*2,2,1,1*}:** yield 10%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, J = 8.4, 1.1, 2H), 7.46 (s, 1H), 7.41 (dd, J = 13.6, 6.4, 3H), 7.34 (dd, J = 13.3, 7.4, 2H), 7.08 (d, J = 7.8, 1H), 7.01 (d, J = 9.3, 1H), 6.38 (s, 1H), 6.34 (s, 1H), 5.64 (d, J = 8.4, 1H), 4.00−3.92 (m, 5H), 3.92−3.84 (m, 4H), 3.80 (s, 3H), 1.98 (t, J = 12.9, 2H), 1.71 (d, J = 9.7, 3H), 1.37 (ddd, J = 22.1, 13.4, 3.8, 3H), 1.15 (dd, J = 22.8, 10.3, 3H); ESI-MS m/z 558 (MH^+).

2-(Biphenyl-4-yl)-*N*-cyclohexyl-2-(2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*5,1,1,1*}: yield 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.9, 1H), 7.95 (s, 1H), 7.62 (dd, J = 16.6, 7.6, 4H), 7.56−7.32 (m, 7H), 7.32−7.18 (m, 4H), 6.88 (d, J = 8.0, 1H), 6.45 (s, 1H), 5.67 (d, J = 7.9, 1H), 4.02−3.78 (m, 3H), 1.96 (t, J = 11.5, 2H), 1.79−1.64 (m, 3H), 1.44−1.26 (m, 3H), 1.13 (dd, J = 21.9, 10.2, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.66, 167.99, 167.88, 141.87, 136.07, 133.30, 132.82, 132.30, 129.98, 128.86, 127.82, 127.72, 127.14, 125.44, 124.91, 120.31, 77.35, 77.03, 76.71, 61.89, 48.90, 47.64, 32.98, 32.89, 25.46, 24.85, 24.79, 0.02; ESI-MS m/z 468 (MH^+); HR-MS calcd for $C_{29}H_{30}N_3O_3$ $(M + H)^+$ 468.2287, found 468.2310.

2-(8-Chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(2-methoxybiphenyl-4-yl)acetamide 7{*3,2,1,1*}: yield 21%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−7.81 (m, 2H), 7.53 (d, J = 7.6, 2H), 7.47−7.29 (m, 3H), 7.29−7.17 (m, 4H), 7.17−6.88 (m, 2H), 6.37 (d, J = 5.0, 1H), 5.63 (s, 1H), 4.23−3.32 (m, 6H), 1.96 (s, 3H), 1.87−1.43 (m, 7H), 1.35 (d, J = 12.1, 2H), 1.27−0.82 (m, 4H); ESI-MS m/z 532 (MH^+).

2-(8-Chloro-3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(4-(naphthalen-2-yl)phenyl)acetamide 7{*6,1,3,2*}: yield 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.93 (dd, J = 19.8, 11.8, 6H), 7.79 (d, J = 8.3, 3H), 7.72 (dd, J = 8.5, 1.8, 1H), 7.61 (d, J = 8.3, 2H), 7.52 (s, 3H), 7.19 (dd, J = 8.5, 1.9, 1H), 6.91 (d, J = 1.9, 1H), 6.70 (s, 1H), 5.55 (d, J = 8.2, 1H), 4.37−4.22 (m, 1H), 4.02−3.83 (m, 1H), 1.93 (dd, J = 36.3, 20.1, 3H), 1.76−1.62 (m, 4H), 1.41−1.25 (m, 4H), 1.25−1.01 (m, 5H), 0.82−0.58 (m, 2H), 0.44 (dd, J = 10.5, 6.6, 6H); ESI-MS m/z 608 (MH^+).

2-(3′-Acetylbiphenyl-4-yl)-2-(8-chloro-3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexylacetamide 7{*6,1,3,6*}: yield 28%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.95 (t, J = 7.2, 2H), 7.78 (d, J = 7.8, 1H), 7.70 (dd, J = 12.4, 7.1, 3H), 7.63−7.50 (m, 3H), 7.19 (dd, J = 8.5, 1.9, 1H), 6.89 (d, J = 1.8, 1H), 6.67 (s, 1H), 5.54 (d, J = 8.1, 1H), 4.25 (dd, J = 10.5, 5.8, 1H), 4.00−3.82 (m, 1H), 2.73−2.58 (m, 3H), 1.95 (t, J = 12.8, 2H), 1.68 (d, J = 13.3, 3H), 1.43−1.25 (m, 4H), 1.14 (dt, J = 34.0, 10.3, 5H), 0.75−0.58 (m, 2H), 0.43 (dd, J = 16.0, 6.6, 6H); Isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 33.5, 1H), 8.04−7.86 (m, 2H), 7.86−7.72 (m, 2H),

7.72−7.57 (m, 2H), 7.51 (td, J = 8.1, 4.2, 3H), 7.39 (dd, J = 25.6, 8.5, 1H), 7.23−6.97 (m, 1H), 6.97−6.61 (m, 2H), 6.34 (s, 1H), 5.88 (d, J = 6.3, 1H), 4.32 (dd, J = 11.0, 3.4, 1H), 3.88 (dd, J = 11.4, 7.2, 1H), 2.73−2.56 (m, 3H), 2.09−1.89 (m, 2H), 1.88−1.66 (m, 3H), 1.50−1.29 (m, 4H), 1.28−1.04 (m, 4H), 1.02−0.79 (m, 3H), 0.73 (dd, J = 13.4, 7.5, 3H), 0.49−0.17 (m, 1H); ESI-MS m/z 600 (MH^+).

2-(4-(Benzo[*b*]thiophen-2-yl)-3-methoxyphenyl)-*N*-cyclohexyl-2-(8-fluoro-3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*7,2,3,7*}: yield 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.95−7.54 (m, 6H), 7.43−7.24 (m, 5H), 7.18−6.97 (m, 3H), 6.87 (ddd, J = 13.2, 12.1, 7.2, 1H), 6.36 (d, J = 27.6, 1H), 6.00 (s, 1H), 4.51−4.23 (m, 1H), 4.15−3.80 (m, 5H), 1.99 (s, 2H), 1.88−1.67 (m, 3H), 1.52−1.29 (m, 4H), 1.29−1.05 (m, 4H), 0.99−0.56 (m, 6H), 0.51−0.26 (m, 1H); Isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 4H), 7.47−7.28 (m, 2H), 7.15 (s, 2H), 7.08−6.70 (m, 2H), 6.22 (d, J = 300.5, 1H), 5.53 (d, J = 8.4, 1H), 4.54−4.24 (m, 1H), 3.93 (d, J = 50.7, 4H), 2.34−2.10 (m, 1H), 2.04−1.72 (m, 3H), 1.61 (d, J = 43.0, 9H), 1.45−1.05 (m, 7H), 1.05−0.32 (m, 8H), 0.15 (s, 1H); ESI-MS m/z 628 (MH^+).

***N*-Cyclohexyl-2-(8-fluoro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(4-(naphthalen-2-yl)phenyl)acetamide 7{*7,1,1,2*}:** yield 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.88 (s, 4H), 7.72 (d, J = 23.0, 5H), 7.58−7.34 (m, 6H), 7.03 (d, J = 23.7, 1H), 6.86 (s, 1H), 6.45 (s, 1H), 5.67 (s, 1H), 4.17−3.73 (m, 4H), 1.96 (d, J = 14.9, 2H), 1.66 (dd, J = 35.4, 9.9, 9H), 1.38 (s, 3H), 1.16 (dd, J = 16.0, 7.5, 4H); ESI-MS m/z 536 (MH^+).

2-(4-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxyphenyl)-*N*-cyclohexyl-2-(2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*5,2,1,3*}: yield 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 6.4, 2H), 7.44 (t, J = 7.6, 1H), 7.37−7.20 (m, 4H), 7.12−7.03 (m, 2H), 7.03−6.95 (m, 2H), 6.91 (d, J = 8.0, 1H), 6.85 (d, J = 8.0, 1H), 6.40 (s, 1H), 5.99 (s, 2H), 5.70 (d, J = 7.9, 1H), 4.05−3.83 (m, 3H), 3.80 (s, 3H), 1.97 (t, J = 13.1, 2H), 1.74−1.56 (m, 4H), 1.35 (dd, J = 16.8, 7.6, 2H), 1.24−1.04 (m, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 170.81, 168.07, 167.85, 156.82, 147.25, 146.87, 136.14, 134.45, 132.86, 132.25, 131.50, 131.22, 131.06, 125.43, 124.91, 122.97, 121.84, 120.38, 112.34, 110.18, 108.13, 101.06, 62.33, 55.75, 48.91, 47.71, 33.00, 32.84, 25.44, 24.85, 24.79, −13.05; ESI-MS m/z 542 (MH^+); HR-MS calcd for $C_{31}H_{32}N_3O_6$ $(M + H)^+$ 542.2291, found 542.2293.

2-(8-Chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(2-methoxy-4′-vinylbiphenyl-4-yl)-acetamide 7{*6,2,1,4*}: yield 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.69 (m, 2H), 7.48 (dt, J = 13.7, 8.3, 4H), 7.41−7.31 (m, 1H), 7.25−7.11 (m, 2H), 7.10−6.85 (m, 3H), 6.75 (ddd, J = 17.6, 10.9, 2.9, 1H), 6.36 (s, 0H), 5.91−5.73 (m, 1H), 5.65 (d, J = 7.7, 1H), 5.28 (dd, J = 10.9, 7.6, 1H), 4.05−3.71 (m, 6H), 1.98 (d, J = 15.3, 3H), 1.70 (d, J = 9.8, 3H), 1.32 (dd, J = 23.8, 11.4, 2H), 1.17 (dd, J = 24.2, 15.2, 4H); ESI-MS m/z 558 (MH^+).

***N*-Cyclohexyl-2-(8-fluoro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(4-(furan-2-yl)-3-methoxyphenyl)acetamide 7{*7,2,1,5*}:** yield 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.87 (d, J = 8.0, 1H), 7.69 (dd, J = 8.9, 2.7, 1H), 7.49 (t, J = 10.2, 1H), 7.26 (s, 3H), 7.19−7.03 (m, 2H), 7.03−6.93 (m, 2H), 6.85 (dd, J = 8.5, 4.3, 1H), 6.50 (dd, J = 3.3, 1.8, 1H), 6.34 (s, 1H), 5.64 (d, J = 6.8, 1H), 4.09−3.75 (m, 6H), 2.64 (s, 1H), 1.95 (s, 3H), 1.68 (s, 3H), 1.46−1.26 (m, 2H), 1.13 (dd, J = 20.1, 9.2, 3H); ESI-MS m/z 506 (MH^+).

2-(4-(Benzo[*b*]thiophen-2-yl)-3-methoxyphenyl)-*N*-cyclohexyl-2-(8-fluoro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*7,2,1,7*}: yield 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.90−7.63 (m, 6H), 7.33 (pd, J = 7.1, 1.3, 2H), 7.16−7.03 (m, 3H), 6.88 (dd, J = 8.8, 4.4, 1H), 6.35 (s, 1H), 5.65 (d, J = 7.9, 1H), 3.96 (s, 5H), 3.92−3.79 (m, 2H), 1.97 (t, J = 14.0, 3H), 1.75−1.66 (m, 4H), 1.36 (dd, J = 15.9, 7.6, 3H), 1.23−1.03 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.41, 167.48, 156.73, 140.03, 138.92, 134.90, 132.40, 129.94, 124.42, 124.31, 123.66, 123.22, 122.04, 121.88, 112.88, 107.38, 62.28, 55.88, 49.00, 45.11, 33.01, 25.41, 24.83; ESI-MS m/z 572 (MH^+); HR-MS calcd for $C_{32}H_{31}FN_3O_4S$ $(M + H)^+$ 572.2019, found 572.2023.

2-(3′-Acetylbiphenyl-4-yl)-*N*-cyclohexyl-2-(3-(4-hydroxyphenyl)-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*1,1,5,6*}: yield 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.92 (d, J = 7.8, 1H), 7.84 (s, 1H), 7.73 (d, J = 7.8, 1H), 7.70−7.63 (m, 3H), 7.60 (d, J = 8.0, 2H), 7.52 (t, J = 7.8, 1H), 7.18 (t, J = 7.2, 1H), 6.97 (dd, J = 15.5, 8.0, 1H), 6.86−6.54 (m, 4H), 6.41 (d, J = 8.4, 2H), 5.67 (d, J = 7.7, 1H), 5.41 (s, 1H), 5.06 (s, 1H), 3.93 (d, J = 8.0, 1H), 2.63 (d, J = 11.7, 4H), 1.96 (d, J = 12.0, 2H), 1.67 (d, J = 9.2, 3H), 1.33 (d, J = 9.3, 3H), 1.12 (d, J = 7.2, 3H); ESI-MS m/z 602 (MH^+).

2-(4-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxyphenyl)-*N*-cyclohexyl-2-(3-(4-hydroxyphenyl)-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*1,2,5,3*}: yield 15%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.62 (m, 2H), 7.62−7.35 (m, 3H), 7.34−7.26 (m, 2H), 7.23−7.06 (m, 2H), 7.06−6.87 (m, 3H), 6.87−6.71 (m, 3H), 6.71−6.52 (m, 2H), 6.41 (d, J = 8.1, 2H), 5.97 (s, 2H), 5.62 (d, J = 7.9, 1H), 5.42 (s, 1H), 5.19−4.90 (m, 1H), 3.76 (s, 5H), 2.62 (s, 1H), 1.96 (s, 2H), 1.67 (s, 3H), 1.34 (d, J = 9.1, 2H), 1.24−1.00 (m, 3H); ESI-MS m/z 634 (MH^+).

2-(3′-Acetylbiphenyl-4-yl)-*N*-cyclohexyl-2-(3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*1,1,4,6*}: yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.97 (dd, J = 13.6, 7.2, 2H), 7.78 (d, J = 7.8, 1H), 7.69 (dd, J = 11.8, 6.5, 4H), 7.65−7.51 (m, 4H), 7.45 (dd, J = 12.1, 4.6, 2H), 7.23 (t, J = 7.7, 1H), 6.87 (d, J = 7.9, 1H), 6.68 (s, 1H), 5.62 (d, J = 8.1, 1H), 4.25 (dd, J = 10.0, 5.5, 1H), 3.99−3.83 (m, 1H), 2.73−2.56 (m, 4H), 1.95 (s, 3H), 1.68 (d, J = 13.1, 3H), 1.42−1.24 (m, 4H), 1.23−1.03 (m, 5H), 0.66 (ddd, J = 16.6, 11.1, 6.2, 2H), 0.42 (dd, J = 8.0, 6.7, 6H); ESI-MS m/z 566 (MH^+); HR-MS calcd for $C_{35}H_{40}N_3O_4$ $(M + H)^+$ 566.3019, found 566.3008.

2-(8-Chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(2-methoxy-4′-vinylbiphenyl-4-yl)-acetamide 7{*3,2,1,4*}: yield 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.5, 1H), 7.84 (s, 1H), 7.57 - 7.48 (m, 2H), 7.45 (d, J = 8.3, 2H), 7.34 (t, J = 12.3, 1H), 7.24

(dd, J = 8.5, 1.8, 1H), 7.07 (dd, J = 7.8, 1.4, 1H), 7.00 (d, J = 6.4, 1H), 6.95 (d, J = 1.8, 1H), 6.75 (dd, J = 17.6, 10.9, 1H), 6.37 (s, 1H), 5.79 (d, J = 17.6, 1H), 5.63 (d, J = 8.1, 1H), 5.27 (d, J = 10.9, 1H), 4.04−3.84 (m, 3H), 3.81 (s, 3H), 1.97 (t, J = 14.0, 2H), 1.67 (dd, J = 18.7, 15.0, 8H), 1.44−1.27 (m, 2H), 1.25−1.06 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.21, 167.71, 167.27, 157.05, 138.75, 137.03, 136.56, 133.77, 131.29, 129.64, 125.94, 125.24, 123.90, 121.94, 120.15, 113.96, 112.42, 62.49, 55.79, 48.98, 47.55, 33.01, 32.87, 25.43, 24.79, 0.02; ESI-MS m/z 558 (MH^+).

2-(7-Chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(4-(furan-2-yl)-3-methoxyphenyl)-acetamide 7{*4,2,1,5*}: yield 17%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−7.95 (m, 2H), 7.88 (d, J = 8.0, 1H), 7.47 (d, J = 1.3, 1H), 7.37 (dd, J = 8.6, 2.4, 1H), 7.06 (d, J = 9.3, 1H), 7.03−6.93 (m, 2H), 6.83 (d, J = 8.6, 1H), 6.50 (dd, J = 3.3, 1.8, 1H), 6.33 (s, 1H), 5.60 (d, J = 8.0, 1H), 4.06−3.75 (m, 7H), 1.96 (s, 3H), 1.61 (d, J = 16.7, 3H), 1.46−1.26 (m, 3H), 1.24−1.02 (m, 3H); ESI-MS m/z 522 (MH^+).

2-(3′-Acetyl-2-methoxybiphenyl-4-yl)-2-(7-chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexylacetamide 7{*4,2,1,6*}: yield 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.11 (s, 1H), 7.98 (d, J = 2.4, 1H), 7.93 (d, J = 7.8, 1H), 7.73 (d, J = 7.7, 1H), 7.50 (t, J = 7.8, 2H), 7.42−7.29 (m, 2H), 7.09 (dd, J = 7.8, 1.2, 1H), 7.04 (s, 1H), 6.87 (d, J = 8.6, 1H), 6.37 (s, 1H), 5.71 (d, J = 8.0, 1H), 3.96 (d, J = 1.8, 2H), 3.89 (t, J = 3.9, 1H), 3.80 (s, 3H), 2.72−2.56 (m, 4H), 1.97 (t, J = 11.3, 3H), 1.71 (dd, J = 9.1, 4.3, 3H), 1.61 (d, J = 13.3, 1H), 1.47−1.26 (m, 2H), 1.26−1.05 (m, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 198.15, 170.47, 167.58, 166.84, 156.94, 138.08, 137.06, 135.07, 134.71, 134.23, 132.89, 131.82, 131.38, 130.50, 129.36, 128.33, 127.31, 126.67, 122.00, 121.94, 112.42, 62.38, 55.81, 48.99, 47.56, 33.00, 32.84, 26.77, 25.42, 24.83, 24.78; ESI-MS m/z 574 (MH^+); HR-MS calcd for $C_{32}H_{33}N_3O_5Cl$ 574.2019 $(M + H)^+$ found 574.2089.

2-(3-Benzyl-7-chloro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(3-methoxy-4-(naphthalen-2-yl)phenyl)acetamide 7{*4,2,2,2*}: yield 23%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 2.5, 1H), 7.98 (s, 2H), 7.94−7.80 (m, 3H), 7.69 (dd, J = 8.6, 1.6, 1H), 7.60−7.35 (m, 4H), 7.19−7.03 (m, 3H), 7.03−6.93 (m, 1H), 6.86 (dd, J = 6.8, 5.1, 2H), 6.54 (dd, J = 9.5, 7.7, 2H), 5.41 (d, J = 8.3, 1H), 4.52 (t, J = 8.4, 1H), 4.02−3.64 (m, 5H), 2.62 (dd, J = 13.9, 8.5, 1H), 2.36 (dd, J = 13.6, 8.1, 1H), 1.92 (s, 2H), 1.64 (s, 3H), 1.38−1.18 (m, 3H), 1.10 (dd, J = 24.1, 12.1, 3H); ESI-MS m/z 672 (MH^+); HR-MS calcd for $C_{41}H_{39}N_3O_4Cl$ $(M + H)^+$ 672.2629, found 672.2621.

2-(4-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxyphenyl)-*N*-cyclohexyl-2-(3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*5,2,3,3*}: yield 24%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 7.9, 1.4, 1H), 7.61−7.48 (m, 2H), 7.43 (dt, J = 16.7, 7.1, 2H), 7.31 (d, J = 7.8, 2H), 7.23 (t, J = 7.6, 1H), 7.17−7.10 (m, 1H), 7.10−7.03 (m, 2H), 7.03−6.97 (m, 2H), 6.97−6.91 (m, 1H), 6.87 (dd, J = 14.8, 7.1, 3H), 6.65 (s, 1H), 6.00 (dd, J = 6.3, 2.7, 4H), 5.56 (d, J = 8.2, 1H), 4.37−4.17 (m, 1H), 4.00−3.74 (m, 5H), 1.96 (s, 2H), 1.68 (d, J = 9.0, 2H), 1.42−1.24 (m, 4H), 1.23−1.03 (m, 4H), 0.74−0.61 (m, 1H), 0.44 (dd, J = 6.5, 2.7, 5H); ESI-MS m/z 598 (MH^+); HR-MS calcd for $C_{35}H_{40}N_3O_6$ $(M + H)^+$ 598.2917, found 598.2926.

***N*-Cyclohexyl-2-(8-fluoro-3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(2-methoxy-4′-vinylbiphenyl-4-yl)acetamide 7{*7,2,3,4*}:** yield 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 9.0, 3.0, 1H), 7.61−7.41 (m, 6H), 7.37 (d, J = 7.7, 2H), 7.17 (dd, J = 16.0, 8.7, 2H), 7.11−6.95 (m, 2H), 6.85 (dd, J = 8.8, 4.5, 1H), 6.81−6.67 (m, 2H), 6.64 (d, J = 7.9, 1H), 5.79 (d, J = 17.5, 1H), 5.52 (d, J = 7.9, 1H), 5.27 (d, J = 10.8, 1H), 4.35 - 4.20 (m, 1H), 3.92 (s, 1H), 3.86−3.76 (m, 3H), 1.96 (s, 2H), 1.66 (s, 2H), 1.29 (dd, J = 11.3, 8.4, 4H), 1.24−1.04 (m, 5H), 1.04−0.85 (m, 2H), 0.69 (dd, J = 18.6, 13.1, 1H), 0.46 (dd, J = 6.4, 5.0, 5H); ESI-MS m/z 598 (MH^+).

2-(4-(Benzo[*b*]thiophen-2-yl)phenyl)-*N*-cyclohexyl-2-(3-(4-hydroxyphenyl)-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*1,1,5,7*}: yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.60 (m, 7H), 7.55 (d, J = 6.9, 1H), 7.36 (td, J = 13.0, 6.8, 3H), 7.20 (d, J = 7.0, 1H), 7.06−6.89 (m, 1H), 6.75 (d, J = 7.3, 2H), 6.67 (d, J = 8.1, 2H), 6.42 (d, J = 8.6, 2H), 5.63 (s, 1H), 5.43 (s, 1H), 3.95 (s, 1H), 2.64 (s, 3H), 1.97 (s, 2H), 1.68 (s, 5H), 1.35 (s, 3H), 1.14 (d, J = 9.1, 3H); ESI-MS m/z 616 (MH^+); HR-MS calcd for $C_{37}H_{34}N_3O_4S$ $(M + H)^+$ 616.2270, found 616.2274.

***N*-Cyclohexyl-2-(3-(4-hydroxyphenyl)-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(2-methoxy-4′-vinylbiphenyl-4-yl)acetamide 7{*1,2,5,4*}:** yield 12%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 22.7, 15.4, 3H), 7.58−7.37 (m, 6H), 7.32 (d, J = 7.8, 2H), 7.18 (dd, J = 20.0, 11.1, 3H), 6.97 (dd, J = 13.6, 6.0, 1H), 6.84−6.67 (m, 4H), 6.64 (d, J = 4.4, 2H), 6.41 (d, J = 8.7, 2H), 5.77 (d, J = 17.6, 1H), 5.60 (d, J = 8.3, 1H), 5.44 (s, 1H), 5.25 (d, J = 10.9, 1H), 4.63 (s, 1H), 3.97 (s, 1H), 3.77 (s, 3H), 1.96 (s, 2H), 1.66 (s, 3H), 1.34 (d, J = 9.4, 2H), 1.21−1.02 (m, 3H); ESI-MS m/z 616 (MH^+).

2-(4-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxyphenyl)-*N*-cyclohexyl-2-(7,8-dimethoxy-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)acetamide 7{*2,2,1,3*}: yield 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.54−7.41 (m, 1H), 7.37−7.24 (m, 2H), 7.01 (dd, J = 25.7, 12.3, 4H), 6.88 (t, J = 13.5, 1H), 6.39 (d, J = 16.5, 2H), 6.10−5.94 (m, 2H), 5.81 (s, 1H), 3.93 (d, J = 10.9, 5H), 3.81 (t, J = 17.9, 6H), 1.96 (d, J = 12.4, 2H), 1.66 (dd, J = 35.7, 11.2, 3H), 1.37 (d, J = 9.3, 2H), 1.27−1.03 (m, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 167.94, 156.79, 152.74, 147.26, 146.86, 146.28, 134.56, 131.46, 131.15, 130.93, 122.93, 121.80, 117.21, 113.13, 112.35, 110.13, 108.12, 103.27, 101.06, 56.25, 56.17, 55.74, 48.88, 33.00, 32.83, 25.44, 24.85, 24.79; ESI-MS m/z 602 (MH^+); HR-MS calcd for $C_{33}H_{36}N_3O_8$ $(M + H)^+$ 602.2502, found 602.2507.

***N*-Cyclohexyl-2-(8-fluoro-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(4-(furan-2-yl)phenyl)acetamide 7{*7,1,1,5*}:** yield 24%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1, 4H), 7.68 (s, 2H), 7.52 (d, J = 15.9, 3H), 7.45 (d, J = 8.3, 3H), 7.19 (s, 2H), 6.89 (dd, J = 8.7, 4.4, 2H), 6.72 (d, J = 3.2, 1H), 6.51 (dd, J = 3.2, 1.7, 1H),

6.38 (s, 1H), 5.59 (d, J = 7.9, 1H), 3.95 (s, 5H), 1.98 (s, 4H), 1.70 (s, 8H), 1.39 (d, J = 12.8, 5H), 1.17 (d, J = 11.4, 6H); Isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.87 (m, 4H), 7.70 (dd, J = 27.4, 11.7, 6H), 7.40 (d, J = 7.5, 1H), 7.10 (dd, J = 8.7, 4.5, 1H), 6.94 (d, J = 3.3, 1H), 6.72 (dd, J = 3.4, 1.8, 1H), 6.60 (s, 1H), 5.76 (d, J = 7.5, 1H), 4.16 (s, 4H), 2.19 (s, 3H), 1.93 (s, 3H), 1.59 (d, J = 9.5, 4H), 1.38 (d, J = 11.8, 5H); ESI-MS m/z 476 (MH^+).

2-(8-Chloro-3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(2-methoxybiphenyl-4-yl)acetamide 7{*3,2,4,1*}: yield 15%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.5, 1H), 7.61 (s, 1H), 7.52 (dd, J = 9.9, 8.3, 2H), 7.44 (t, J = 7.5, 2H), 7.37 (t, J = 7.5, 2H), 7.22 (dd, J = 8.5, 1.9, 1H), 7.17 (d, J = 7.8, 1H), 7.10 (s, 1H), 6.90 (d, J = 1.9, 1H), 6.68 (s, 1H), 5.53 (d, J = 8.6, 1H), 4.31 (dd, J = 10.7, 5.5, 1H), 4.10−3.75 (m, 6H), 2.06−1.89 (m, 3H), 1.68 (s, 4H), 1.44−1.27 (m, 5H), 1.27−1.07 (m, 5H), 0.79−0.66 (m, 2H), 0.49 (dd, J = 8.4, 6.6, 5H); ESI-MS m/z 588 (MH^+).

2-(4-(Benzo[*b*]thiophen-2-yl)-3-methoxyphenyl)-2-(8-chloro-3-isobutyl-2,5-dioxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexylacetamide 7{*3,2,4,7*}: yield 21%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.5, 1H), 7.82 (ddd, J = 21.2, 12.9, 6.6, 7H), 7.42−7.29 (m, 6H), 7.25−7.08 (m, 4H), 6.92 (d, J = 1.7, 1H), 6.64 (s, 1H), 5.57 (d, J = 8.1, 1H), 4.33 (dd, J = 10.6, 5.6, 1H), 4.10−3.82 (m, 5H), 2.07−1.86 (m, 3H), 1.70 (d, J = 14.6, 4H), 1.33 (ddd, J = 22.9, 12.5, 7.4, 4H), 1.19 (ddd, J = 24.2, 13.1, 5.3, 5H), 1.01 (dd, J = 8.9, 6.4, 1H), 0.86−0.65 (m, 2H), 0.50 (d, J = 6.5, 7H); Isomer^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, J = 10.1, 1H), 7.92−7.75 (m, 5H), 7.72 (d, J = 7.7, 1H), 7.43−7.30 (m, 3H), 7.19 (d, J = 7.9, 1H), 7.13−7.02 (m, 2H), 6.89 (d, J = 1.8, 1H), 6.33 (s, 1H), 5.89 (s, 1H), 4.37 (dd, J = 11.6, 3.0, 1H), 4.05−3.82 (m, 5H), 2.00 (s, 3H), 1.90−1.79 (m, 1H), 1.79−1.69 (m, 3H), 1.52−1.31 (m, 5H), 1.29−1.10 (m, 4H), 0.91 (d, J = 6.4, 4H), 0.75 (d, J = 6.5, 4H); ESI-MS m/z 644 (MH^+).

2-(3-Benzyl-8-chloro-2,3-dihydro-2,5-dioxo-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(2-methoxybiphenyl-4-yl)acetamide 7{*6,2,2,1*}: yield 15%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.05 (dd, J = 8.5, 6.2, 1H), 7.68−7.40 (m, 3H), 7.40−7.15 (m, 7H), 7.15−6.91 (m, 3H), 6.84 (dd, J = 9.8, 4.5, 1H), 6.48 (t, J = 24.7, 1H), 5.99−5.30 (m, 1H), 4.65−4.35 (m, 1H), 3.73 (d, J = 10.1, 3H), 3.45 (dt, J = 25.8, 11.7, 1H), 2.62 (s, 1H), 2.41−2.18 (m, 1H), 1.88 (s, 2H), 1.67 (d, J = 34.3, 6H), 1.49−0.90 (m, 6H); ESI-MS m/z 622 (MH^+).

2-(3-Benzyl-2,3-dihydro-2,5-dioxo-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(2-methoxybiphenyl-4-yl)acetamide 7{*5,2,2,1*}: yield 20%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−7.89 (m, 2H), 7.66−7.41 (m, 3H), 7.41−7.34 (m, 1H), 7.34−7.24 (m, 5H), 7.19 (d, J = 7.2, 2H), 7.11−7.03 (m, 1H), 7.00 (d, J = 8.7, 1H), 6.86 (dd, J = 22.5, 6.9, 1H), 6.48 (d, J = 25.1, 1H), 6.03−5.34 (m, 1H), 4.52 (ddd, J = 50.5, 26.6, 18.1, 1H), 4.05−3.62 (m, 4H), 3.52−3.28 (m, 1H), 2.62 (s, 1H), 2.33 (dd, J = 13.6, 8.2, 1H), 2.20−1.80 (m, 2H), 1.57 (s, 8H), 1.49−1.15 (m, 4H), 1.15−0.88 (m, 1H); ESI-MS m/z 588 (MH^+).

2-(3-Benzyl-8-fluoro-2,3-dihydro-2,5-dioxo-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-*N*-cyclohexyl-2-(2-methoxybiphenyl-4-yl)acetamide 7{*7,2,2,1*}: yield 18%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 43.2, 1H), 7.79 (dd, J = 5.6, 3.4, 1H), 7.64−7.41 (m, 3H), 7.41−7.23 (m, 6H), 7.23−6.93 (m, 5H), 6.77 (d, J = 68.3, 2H), 6.61−6.32 (m, 2H), 5.59 (dt, J = 117.2, 21.9, 1H), 4.70−4.41 (m, 1H), 3.75 (dd, J = 15.4, 8.7, 4H), 3.55−3.19 (m, 1H), 2.74−2.49 (m, 1H), 2.29 (dd, J = 13.6, 7.8, 0H), 1.89 (s, 2H), 1.66 (d, J = 48.5, 7H), 1.47−0.85 (m, 6H); ESI-MS m/z 606 (MH^+).

***N*-Cyclohexyl-2-(2,3-dihydro-3-isobutyl-2,5-dioxo-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl)-2-(2-methoxybiphenyl-4-yl)acetamide 7{*1,2,4,1*}:** yield 17%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 15.7, 8.0, 1H), 7.83 (d, J = 19.5, 1H), 7.54 (d, J = 7.9, 1H), 7.50−7.30 (m, 4H), 7.29−7.12 (m, 4H), 7.07 (dd, J = 17.0, 9.2, 1H), 6.95−6.78 (m, 1H), 6.51 (d, J = 126.6, 1H), 5.73 (dd, J = 102.3, 7.6, 1H), 4.33 (d, J = 31.6, 1H), 4.12 (d, J = 7.2, 0H), 3.88 (d, J = 21.5, 1H), 3.85−3.64 (m, 2H), 2.01 (dd, J = 28.1, 7.3, 3H), 1.89−1.50 (m, 6H), 1.49−1.01 (m, 8H), 0.97−0.79 (m, 2H), 0.75−0.60 (m, 1H), 0.53−0.34 (m, 2H); ESI-MS m/z 554 (MH^+).

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Supporting Information Available. LC/MS and HR-MS and ^{1}H and ^{13}C NMR data for selected intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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