# Solid-Phase Synthesis of 3,4,5-Substituted 1,5-Benzodiazepin-2-ones†

Jung Lee,* Diane Gauthier, and Ralph A. Rivero

*The R.W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477*

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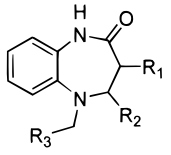
The preparation of 3,4,5-substituted 8-carboxamido-1,5-benzodiazepin-2-ones using a solid-phase synthetic method is described. 4-Fluoro-3-nitrobenzoic acid is tethered to a solid support via the acid group. Aromatic substitution of the aryl fluoride with either an α- or *β*-substituted *β*-amino ester is carried out in the presence of DIEA in DMF. The reduction of the aryl nitro group is accomplished in the presence of $SnCl_2 \cdot H_2O$. Hydrolysis of the ester is carried out in the presence of a heterogeneous mixture of 1 N NaOH/THF (1:1). The resulting aniline acid is cyclized to form the benzodiazepinone skeleton with DIC and HOBt. Selective alkylation at the N-5 position of the benzodiazepinone is accomplished with alkyl halides in the presence of $K_2CO_3$ in acetone. The desired products are cleaved from solid supports and obtained in 46−98% isolated yields.

## Introduction

During the last 6 years, development of solid-phase synthetic methods has been a major focus for many chemists.[1] The ability to synthesize a large number of small molecules in a short period of time has facilitated the high-throughput screening programs in most pharmaceutical companies. Even though the addition of new compounds has accelerated tremendously, the important issue of creating the diversity of the chemical libraries still remains. In developing a solid-phase synthetic method for a heterocycle, one would be able to make thousands of molecules, but the essential scaffold remains the same. Having structural diversity in chemical libraries would provide a better chance of finding a novel ligand during high-throughput screening. Therefore, the development of a solid-phase synthetic method that could be used to prepare a variety of chemical templates remains as an important task. Previously, Gallop and co-workers have demonstrated this approach in one example.[2] In their work, a resin-bound imine intermediate has been used to prepare a variety of chemical templates, such as pyrrolidines,[2a] thiazolidinones,[2b] and *β*-lactams.[2c] More recently, we have reported along with Phillips and coworkers the solid-phase synthesis of benzimidazoles (five-member heterocycle),[3a] 1,3-dialkylbenzimidazole-2-ones (five-member heterocycle),[3b] 1-alkyl-2-alkylthiobenzimidazole (five-member heterocycle),[3c] and quinoxalin-2-ones (six-member heterocycle)[3d] from a common intermediate, the resin-bound 4-fluoro-3-nitrobenzoic acid. Now, we are pleased to report the solid-phase synthesis of 3,4,5-trisubstitued 8-carboxamido-1,5-benzodiazepin-2-ones, seven-memebered heterocycles, from a common intermediate.[4]

Benzodiazepines[5] have been an important pharmacophore in the pharmaceutical industry. The therapeutic applications of benzodiazepines include anxiolytics,[6a] antiarrhythmics,[6b] vasopressin antagonists,[6c] HIV reverse transcriptase inhibitors,[6d] and cholecystokinin antagonists.[6e] In fact, the first heterocyclic templates prepared on a solid support were 1,4-benzodiazepines.[7] Since then there have been numerous reports on the synthesis of similar skeletons.[8] To test the feasibility of preparing the 1,5-benzodiazepin-2-ones **1** on a solid support, we targeted the preparation 35 compounds with variation of three diversity elements.




**1**

## Results and Discussion

Our synthetic strategy involved a route similar to the one reported previously and is shown in Scheme 1.[3d] We initially decided to attach the phenyl ring of the benzodiazepinone to a solid support and then build the heterocyclic ring on the support. The attachment of the phenyl ring to the solid support was to be accomplished

* To whom correspondence should be addressed. Tel: (215)-628-5228. Fax: (215)-628-3297. E-mail: jlee@prius.jnj.com.

† Dedicated to Professor Satoru Masamune on the occasion of his 70th birthday.

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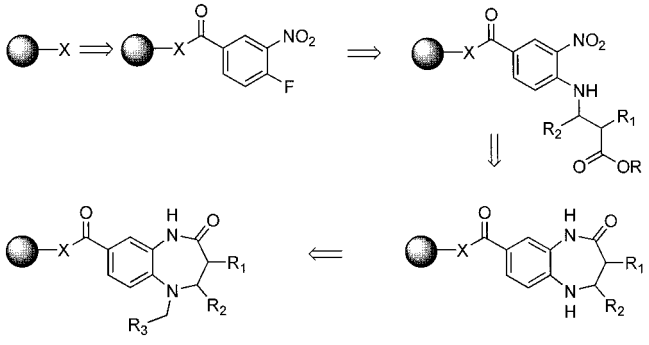
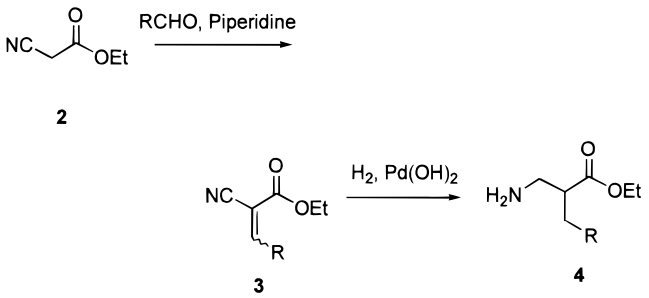
**Scheme 1**



**Scheme 2**



through the acid function of 4-fluoro-3-nitrobenzoic acid.[9] In our previous paper,[3d] we had used α-amino esters to form the basic skeleton of the six-membered ring of quinoxalinones. Therefore, utilizing *β*-amino esters seemed to be the obvious choice to construct the basic skeleton of the seven-membered benzodiazepinones. Because not many substituted *β*-amino esters were commercially available, we decided to employ a simple route[10] to prepare a variety of α-substituted *β*-amino esters, as shown in Scheme 2. After the aromatic substitution of the aryl fluoride with the *β*-amino ester, the stage was set for the formation of the heterocyclic ring of the benzodiazepinones. The reduction of the aryl nitro group and subsequent intramolecular cyclization[11] of the resulting amine with the ester would give the skeleton of benzodiazepinones. Alkylation at the N-5 position of the skeleton with alkyl halides would result in the introduction of one more diversity element in the core structure.

As shown in Scheme 1, a substituent at the *β* position of the *β*-amino ester transforms to the substituent at C-4 position of the benzodiazepinones. We anticipated that the presence of a bulky group at the C-4 position of the benzodiazepinones would cause difficulty in alkylation at the N-5 position due to possible steric hindrance. Therefore, for the preparation of either α- or *β*-substituted *β*-amino esters, we concentrated mostly on the α-substituted *β*-amino esters. After considering the preexisting abundance of starting materials, we chose to prepare the α-substituted *β*-amino esters from ethyl cyanoacetate and aldehydes. The preparation involved two steps as shown in Scheme 2. The Knoevenagel condensation[10] of ethyl cyanoacetate **2** and aldehydes, and subsequent reduction of the resulting acrylic nitrile **3** with Pearlman's catalyst gave the desired α-substituted *β*-amino esters **4** from 43% to 59% overall yields. Surprisingly, the route described above has not been used to prepare α-substituted *β*-amino esters to our knowledge.[12] Full investigation of the synthetic route will be reported elsewhere.[13]

With the *β*-amino esters in hand, the solid-phase synthesis began with removal of the Fmoc-protecting group from Rink-Amide resin with DMF/piperidine (1:1), as shown in the Scheme 3. 4-Fluoro-3-nitrobenzoic acid was then attached to the resultant amino-resin using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and *N*,*N*′-diisopropylethylamine (DIEA). Portions of the product resin **6** were equally divided into seven parts. Each portion of resin was then allowed to react with seven different *β*-amino esters. Hindered *β*-substituted *β*-amino esters, such as ethyl 3-aminobutyrate and methyl 3-amino-3-phenylpropionate, were chosen to observe the effects of any steric hindrance during the course of the synthesis. Aromatic substitution of the activated aryl fluoride **6** with *β*-amino ester was accomplished in the presence of DIEA in DMF for 3 days.

To verify the extent of aromatic substitution, small portions of the resins **7** were treated with 95% TFA for a period of 50 min. The cleaved products were separated from the resins and concentrated. The concentrated products were initially analyzed by LC and then purified by flash chromatography. The initial LC analysis indicated that no starting materials were observed, and the products **8** were greater than 90% pure in all cases. The crude products were then purified by flash chromatography. The purified products were analyzed by LC, MS, and $^1$H and $^{13}$C NMR. In all cases, the analysis confirmed

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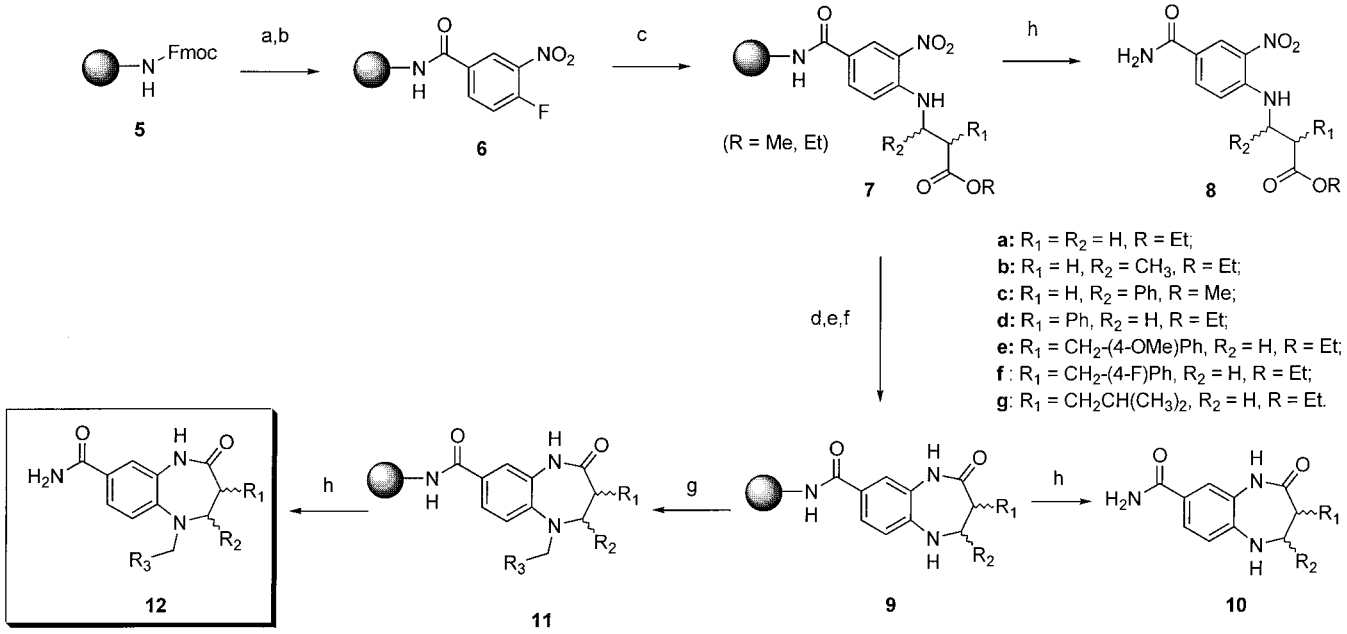
**Scheme 3**[a]




[a] Key: (a) DMF/piperidine (1:1); (b) (4-F-3-$NO_2$)$PhCO_2H$, HATU, DIEA, DMF; (c) $H_2NCH(R_2)CH(R_1)CO_2R$, DIEA, DMF; (d) $SnCl_2 \cdot H_2O$, DMF; (e) 1 N NaOH; THF (1:1); (f) DIC, HOBt, DMF; (g) $R_3CH_2Br$, $K_2CO_3$, $CH_3COCH_3$, 55 °C; (h) TFA/$H_2O$ (95:5).

the structure of the desired product **8**, and the yields ranged from 71 to 96%.

The aryl nitro group of the resin **7** was then reduced with $SnCl_2 \cdot H_2O$.[14] To verify the completion of the reduction, samples of the resins were subjected to the same TFA treatments as before. The crude products were analyzed by LC and MS. The analysis of the products indicated complete reduction of the nitro group. As expected, the intramolecular cyclization observed in the quinoxalinone case did not spontaneously occur at this time. At this point we considered two alternatives for the intramolecular cyclization to form the seven-membered ring.[11] One possibility involved two steps: initial hydrolysis of the ester to form a free acid and then cyclization of the aniline acid with a coupling agent. The other possibility involved direct cyclization of the aniline ester to form the seven-membered ring. Since the latter possibility requires only one step, we focused on the direct cyclization. All attempts[11] with aid of acid, base, heat, or use of various solvents were unfruitful. Even the use of sodium *tert*-butoxide at 60 °C in THF[11d] did not produce the cyclized product. Thus, we turned to the other alternative. After some experiments, we found refluxing the resin in a heterogeneous mixture (1:1) of 1 N NaOH and THF for 24 h provided clean hydrolysis of the ester. The product was analyzed after cleaving from the resin. The characterization of the product with LC, MS, and $^1H$ NMR confirmed the hydrolysis, and the product was obtained in almost quantitative yield. To our delight, the next step involving the intramolecular cyclization of the aniline acid with 1,3-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) proceeded without any problems. To verify the completion of the cyclization, samples of the resins were subjected to the same TFA treatment as before. As before, the crude products were initially analyzed by LC and MS and purified by flash chromatography. The subsequent analysis of the purified materials indicated that a complete intramolecular cyclization occurred in all seven cases and the disubstituted 1,5-benzodiazepin-2-ones **10** were obtained in 55−88% yields.

Once the basic skeleton of 1,5-benzodiazepin-2-ones had been prepared, additional diversity was added to N-5 position of the benzodiazepinones. As we have done previously with quinoxalinones,[3d] the resins containing the benzodiazepinones **9** were treated with alkyl halides. The five-alkyl halides consisted of benzyl bromide, methyl 4-(bromomethyl)benzoate, 1-bromomethyl-3-methoxybenzene, 2-(bromomethyl)naphthalene, and 4-nitrobenzyl bromide. After the resins were treated with the alkyl halides in the presence of $K_2CO_3$ in refluxing acetone for 24 h, the products were cleaved from the resins using the standard cleavage conditions. The crude products were concentrated and then analyzed by LC and MS. In all samples, no dialkylation products were observed. But as expected, when the C-4 position of the benzodiazepinone contained a phenyl group, a trace of unreacted starting material was observed in most of the LC spectra. Interestingly, no variance in reactivity was observed between electron-donating and -withdrawing alkyl halides.

The crude products were subsequently purified by flash chromatography. The chromatographed products were again analyzed by LC, MS, and $^1H$ and $^{13}C$ NMR to confirm structure and purity. The desired products, shown in Table 1, were obtained in 46−98% yields. It is worthy to note that after eight synthetic steps on a solid support 98% yields were obtained in some cases. It certainly demonstrates the efficiency and feasibility of the solid-phase synthetic method developed.

In summary, we have demonstrated that 3,4,5-trisubstituted 8-carboxamido-1,5-benzodiazepin-2-ones can be prepared on a solid support from common building blocks such as $\beta$-amino esters and alkyl halides. So far, we have demonstrated that three different heterocycles could be derived from a common intermediate, the resin-bound

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**Table 1. 3,4,5-Substituted 8-Carboxamido-1,5-benzodiazepin-2-ones**

| | $R_1$ | $R_2$ | $R_3$ | isolated yield[a] (%) |
|---|---|---|---|---|
| **12a** | H | H | Ph | 87 |
| **12b** | H | H | 4-$CO_2$MePh | 75 |
| **12c** | H | H | 3-OMePh | 74 |
| **12d** | H | H | 2-naphthyl | 67 |
| **12e** | H | H | 4-$NO_2$Ph | 54 |
| **12f** | H | $CH_3$ | Ph | 68 |
| **12g** | H | $CH_3$ | 4-$CO_2$MePh | 54 |
| **12h** | H | $CH_3$ | 3-OMePh | 52 |
| **12i** | H | $CH_3$ | 2-naphthyl | 64 |
| **12j** | H | $CH_3$ | 4-$NO_2$Ph | 64 |
| **12k** | H | Ph | Ph | 63 |
| **12l** | H | Ph | 4-$CO_2$MePh | 58 |
| **12m** | H | Ph | 3-OMePh | 46 |
| **12n** | H | Ph | 2-naphthyl | 93 |
| **12o** | H | Ph | 4-$NO_2$Ph | 52 |
| **12p** | Ph | H | Ph | 97 |
| **12q** | Ph | H | 4-$CO_2$MePh | 98 |
| **12r** | Ph | H | 3-OMePh | 98 |
| **12s** | Ph | H | 2-naphthyl | 85 |
| **12t** | Ph | H | 4-$NO_2$Ph | 89 |
| **12u** | $CH_2$(4-OMe)Ph | H | Ph | 67 |
| **12v** | $CH_2$(4-OMe)Ph | H | 4-$CO_2$MePh | 65 |
| **12w** | $CH_2$(4-OMe)Ph | H | 3-OMePh | 72 |
| **12x** | $CH_2$(4-OMe)Ph | H | 2-naphthyl | 74 |
| **12y** | $CH_2$(4-OMe)Ph | H | 4-$NO_2$Ph | 77 |
| **12z** | $CH_2$(4-F)Ph | H | Ph | 51 |
| **12aa** | $CH_2$(4-F)Ph | H | 4-$CO_2$MePh | 63 |
| **12ab** | $CH_2$(4-F)Ph | H | 3-OMePh | 53 |
| **12ac** | $CH_2$(4-F)Ph | H | 2-naphthyl | 63 |
| **12ad** | $CH_2$(4-F)Ph | H | 4-$NO_2$Ph | 47 |
| **12ae** | $CH_2CH(CH_3)_2$ | H | Ph | 59 |
| **12af** | $CH_2CH(CH_3)_2$ | H | 4-$CO_2$MePh | 66 |
| **12ag** | $CH_2CH(CH_3)_2$ | H | 3-OMePh | 63 |
| **12ah** | $CH_2CH(CH_3)_2$ | H | 2-naphthyl | 64 |
| **12ai** | $CH_2CH(CH_3)_2$ | H | 4-$NO_2$Ph | 64 |

[a] Yields are based on support-bound starting material **5**.

4-fluoro-3-nitrobenzoic acid. The heterocycles consist of five-membered (benzimidazole), six-membered (quinoxalinones), and seven-membered (benzodiazepinones) rings. By simple manipulation of building blocks, one can prepare distinctively different heterocyclic templates using essentially one solid-phase synthetic method. Additional templates could be prepared by manipulating different building blocks. These efforts are currently in progress and will be reported in due course.

## Experimental Section

Reagents were purchased from Aldrich, Lancaster, Pfaltz & Bauer, TCI America, Novabiochem, and Bachem Biosciences and used without further purification. $^1$H and $^{13}$C NMR spectra were collected on Bruker AC-300 or DMX 400 FT NMR spectrometers. Chemical shifts are reported with respect to tetramethylsilane (TMS) $\delta_{H,C} = 0.0$ ppm. Spectra were acquired at ambient temperature using DMSO-$d_6$, $CD_3OD$, or $CDCl_3$. Mass spectral analyses were performed on a Fisons instrument (Hewlett-Packard HPLC driven electrospray MS instrument). Analytical HPLC analyses were performed on a Hewlett-Packard liquid chromatography system (YMC column, 4 mm × 50 mm, 4 $\mu$m $C_{18}$, 1.0 mL/min, 8 min gradient from 95% aqueous media (0.1% TFA) to 95% $CH_3CN$ (0.1% TFA), 220 and 260 nm).

**Synthesis of α-Substituted *β*-Amino Esters. Ethyl 2-Cyano-3-(4-fluoro)phenyl-2-propenoate (3a).** To 12.3 mL (116 mmol) of ethyl cyanoacetate were added 140 mL of toluene, 1.52 mL of piperidine, and 12.4 mL (116 mmol) of 4-fluorobenzaldehyde at room temperature. The suspension was allowed to reflux overnight. The next day, the suspension was cooled, and the solvent was removed under the reduced pressure. To the crude solid was then added 200 mL of hexane. The yellow solids were filtered, washed with hexane (3 × 50 mL), and dried to obtain 24.9 g (99% yield) of the α,*β*-unsaturated ester **3a**: mp 90−92 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.21 (1H, s), 8.03 (2H, dd, $J$ = 8.7, 7.0 Hz), 7.20 (2H, t, $J$ = 8.6 Hz), 4.39 (2H, q, $J$ = 7.2, 14.2 Hz), 1.40 (3H, t, $J$ = 7.0 Hz); $^{13}$C NMR (75 MHz, DMSO) $\delta$ 163.6, 162.3, 153.9, 133.4, 127.7, 116.7, 116.4, 102.5, 62.7, 14.1.

**Ethyl 2-Cyano-3-(4-methoxy)phenyl-2-propenoate (3b).** Using the same procedure, from 14.1 mL (116 mmol) of 4-methoxybenzaldehyde, 25.3 g (94% yield) of **3b** was obtained as a yellow solid: mp 81−82 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.15 (1H, s), 7.99 (2H, d, $J$ = 8.8 Hz), 6.98 (2H, $J$ = 8.8 Hz), 4.36 (2H, q, $J$ = 7.1, 14.3 Hz), 3.89 (3H, s), 1.39 (3H, t, $J$ = 7.2 Hz); $^{13}$C NMR (75 MHz, DMSO) $\delta$ 163.6, 162.9, 154.2, 133.5, 124.2, 116.1, 114.6, 99.2, 62.3, 55.5, 14.1.

**Ethyl α-(Aminomethyl)-4-fluorohydrocinnamate (4a).** To 6.58 g (30 mmol) of **3a** were added 80 mL of ethanol, 4.0 mL of the concentrated hydrochloride, and 658 mg of $Pd(OH)_2$ (20 wt % Pd on carbon). The suspension was hydrogenated for 3 days. After 3 days, the crude reaction solution was concentrated under the reduced pressure. To the concentrated crude were then added 125 mL of $CH_2Cl_2$ and 200 mL of 1 N HCl. After separation of the organic layer, the aqueous layer was washed with 2 × 100 mL of $CH_2Cl_2$ and neutralized with a saturated solution of $NaHCO_3$. The neutralized solution was back-extracted with 3 × 100 mL of ethyl acetate. The combined organic layer was dried over $Na_2SO_4$ and concentrated to obtain 3.4 g (43% yield) of a yellow oil: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.24 (2H, dd, $J$ = 5.5, 8.5 Hz), 7.03 (2H, t, $J$ = 8.5 Hz), 4.15 (2H, q, $J$ = 7.1, 14.0 Hz), 3.18−2.89 (5H, m), 1.18 (3H, t, $J$ = 7.1 Hz).

**Ethyl α-(Aminomethyl)-4-methoxyhydrocinnamate (4b).** Using the same procedure, from 11.6 g (50 mmol) of **3b**, 7.5 g (63% yield) of a reddish oil was obtained: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.09 (2H, d, $J$ = 8.5 Hz), 6.82 (2H, d, $J$ = 8.5), 4.07 (2H, q, $J$ = 7.2, 14.3 Hz), 3.74 (3H, s), 2.76 (5H, m), 1.15 (3H, t, $J$ = 7.2 Hz).

**Attachment of 4-Fluoro-3-nitrobenzoic Acid to Rink Amide Resin.** To 20 g of the Rink Amide resin (Novabiochem, 0.67 mmol/g) was added a solution containing 60 mL of each DMF and piperidine at room temperature. The suspension was allowed to mix at room temperature for 50 min. After 50 min, the supernatant was removed. The resin was washed with DMF, MeOH, $CH_2Cl_2$, and $Et_2O$, and then dried in vacuo. To the dried resin were added 9.92 g (53.6 mmol) of 4-fluoro-3-nitrobenzoic acid, 20.4 g (53.6 mmol) of HATU, 18.7 mL (107 mmol) of DIEA, and 100 mL of dry DMF at room temperature. The suspension was allowed to mix at room temperature overnight. The next day, the supernatant was removed. The resin was washed with DMF, MeOH, $CH_2Cl_2$, and $Et_2O$ and then dried in vacuo.

**General Procedure for Aromatic Substitution of the Aryl Fluoride with *β*-Amino Esters.** To each 1 g (approximately 0.67 mmol) of the above resin was added 4 equiv of either α- or *β*-substituted *β*-amino ester (*β*-alanine ethyl ester HCl, ethyl 3-aminobutyrate, methyl 3-amino-3-phenylpropionate, ethyl 3-amino-2-phenylpropionate, ethyl 3-amino-2-benzylpropionate, ethyl 3-amino-2-(4-methoxy)benzylpropionate, ethyl 3-amino-2-(4-fluoro)benzylpropionate, ethyl 2-aminomethyl-4-methylpentanoate), 8 equiv of DIEA, and 5 mL of DMF at room temperature. The suspensions were allowed to mix at room temperature for 3 days. After 3 days, supernatants were removed. The resins were washed with DMF, MeOH, $CH_2Cl_2$, and $Et_2O$ and dried in vacuo. From each of the seven resins, 100 mg was removed to analyze the intermediates. To each 100 mg of the resin was added 1 mL of a solution containing 950 $\mu$L of TFA and 50 $\mu$L of $H_2O$ at ice-bath temperature. The mixtures were slowly warmed to room temperature and allowed to mix for 50 min. After 50 min, the supernatants were removed, and the resins were washed with MeOH (3 × 2 mL). The combined supernatants were concentrated under a stream of nitrogen. The concentrated samples were further dried in vacuo. The crude samples were analyzed by LC and

MS and then purified by flash chromatography. The purified products were weighed and analyzed by LC, MS, and $^1$H and $^{13}$C NMR.

***N*-(2-Nitro-4-carboxamido)phenyl-*β*-alanine Ethyl Ester (8a).** From 100 mg of the resin (before the cleavage of the product) was obtained 18 mg (96% yield) of a yellow solid: mp 195−197 °C; HPLC $t_R$ 5.2 min; $^1$H NMR (300 MHz, DMSO) $\delta$ 8.65 (1H, d, $J$ = 1.9 Hz), 8.45 (1H, t, $J$ = 5.8 Hz), 8.02 (2H, m), 7.30 (1H, s), 7.15 (1H, d, $J$ = 9.2 Hz), 4.08 (2H, q, $J$ = 7.1, 14.3 Hz), 3.67 (2H, m), 2.70 (2H, t, $J$ = 6.6 Hz), 1.18 (3H, t, $J$ = 7.2 Hz); $^{13}$C NMR (75 MHz, DMSO) $\delta$ 173.0, 167.7, 147.9, 136.7, 132.4, 128.2, 122.7, 115.8, 61.9, 34.9, 15.8; MS (ESI) $m/z$ 282 (M + H$^+$).

***N*-(2-Nitro-4-carboxamido)phenyl-3-methylpropionate Ethyl Ester (8b).** From 100 mg of the resin (before the cleavage of the product) was obtained 19 mg (96% yield) of a yellow oil: HPLC $t_R$ 5.5 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.75 (1H,s), 8.46 (1H, d, $J$ = 7.8 Hz), 7.99 (1H, d, $J$ = 9.1 Hz), 7.13 (1H, d, $J$ = 9.1 Hz), 4.31 (1H, m), 4.14 (2H, q, $J$ = 7.2, 14.4 Hz), 2.70 (2H, d, $J$ = 5.8 Hz), 1.38 (3H, d, $J$ = 6.5 Hz), 1.23 (3H, t, $J$ = 7.1 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 172.7, 170.2, 147.4, 136.0, 132.6, 128.3, 121.6, 115.3, 61.9, 47.0 (46.9), 41.6, 20.4, 14.5; MS (ESI) $m/z$ 296 (M + H$^+$).

***N*-(2-Nitro-4-carboxamido)phenyl-3-phenylpropionate Methyl Ester (8c).** From 100 mg of the resin (before the cleavage of the product) was obtained 20 mg (83% yield) of a yellow oil: HPLC $t_R$ 6.0 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 9.08 (1H, d, $J$ = 6.7 Hz), 8.76 (1H, s), 7.83 (1H, d, $J$ = 8.9 Hz), 7.42−7.24 (5H, m), 6.86 (1H, d, $J$ = 9.1 Hz), 5.21 (1H, q, $J$ = 6.4, 12.9 Hz), 3.65 (3H, s), 3.17 (2H, d, $J$ = 6.1 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 171.0, 168.6, 145.7, 140.3, 134.1, 131.6, 128.6, 127.5, 126.4, 125.9, 120.8, 114.7, 54.1, 54.0, 50.9, 41.4; MS (ESI) $m/z$ 344 (M + H$^+$).

***N*-(2-Nitro-4-carboxamido)phenyl-2-phenylpropionate Ethyl Ester (8d).** From 100 mg of the resin (before the cleavage of the product) was obtained 19 mg (76% yield) of a yellow oil: HPLC $t_R$ 6.4 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.70 (1H, d, $J$ = 1.7 Hz), 7.93 (1H, dd, $J$ = 2.2, 9.2 Hz), 7.36−7.27 (5H, m), 7.07 (1H, d, $J$ = 9.2 Hz), 4.23−4.05 (4H, m), 3.78 (1H, q, $J$ = 9.8, 16.6 Hz), 1.18 (3H, t, $J$ = 7.2 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 173.8, 170.2, 148.0, 137.6, 135.9, 132.6, 130.0, 129.2, 129.0, 128.1, 121.8, 115.1, 62.4, 52.0, 46.5, 14.3; MS (ESI) $m/z$ 358 (M + H$^+$).

***N*-(2-Nitro-4-carboxamido)phenyl-2-((4-methoxy)benzyl)propionate Ethyl Ester (8e).** From 100 mg of the resin (before the cleavage of the product) was obtained 19 mg (71% yield) of a yellow oil: HPLC $t_R$ 6.5 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.73 (1H, d, $J$ = 2.1 Hz), 8.50 (1H, m), 7.93 (1H, dd, $J$ = 2.0, 9.0 Hz), 7.12 (2H, d, $J$ = 8.5 Hz), 6.90 (1H, $J$ = 9.1 Hz), 6.83 (1H, d, $J$ = 8.6 Hz), 4.08 (2H, q, $J$ = 7.0, 14.2 Hz), 3.76 (3H, s), 3.73−3.55 (2H, m), 3.12−2.81 (3H, m), 1.15 (3H, t, $J$ = 7.0 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 173.8, 168.7, 158.6, 146.4, 134.4, 131.2, 129.9, 129.5, 126.6, 120.3, 113.5, 60.6, 54.2, 43.4, 34.6, 12.9; MS (ESI) $m/z$ 402 (M + H$^+$).

***N*-(2-Nitro-4-carboxamido)phenyl-2-((4-fluoro)benzyl)-propionate Ethyl Ester (8f).** From 100 mg of the resin (before the cleavage of the product) was obtained 19 mg (76% yield) of a yellow oil: HPLC $t_R$ 6.7 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.73 (1H, d, $J$ = 2.1 Hz), 8.50 (1H, m), 7.25−6.88 (5H, m), 4.07 (2H, q, $J$ = 7.0, 14.2 Hz), 3.67−3.59 (2H, m), 3.12−2.88 (3H, m), 1.13 (3H, m); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 173.6, 168.7, 146.4, 134.4, 132.0, 131.3, 130.3, 126.6, 120.4, 119.7, 114.8, 114.6, 113.5, 60.6, 51.0, 43.6, 34.5, 12.9; MS (ESI) $m/z$ 390 (M + H$^+$).

***N*-(2-Nitro-4-carboxamido)phenyl-2-(2-isobutyl)propionate Ethyl Ester (8 g).** From 100 mg of the resin (before the cleavage of the product) was obtained 19 mg (76% yield) of a yellow oil: HPLC $t_R$ 6.6 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.74 (1H, d, $J$ = 2.1 Hz), 8.44 (1H, m), 7.99 (1H, dd, $J$ = 2.1, 9.0 Hz), 7.09 (1H, dd, $J$ = 1.7, 9.1 Hz), 4.15 (2H, q, $J$ = 7.2, 14.5 Hz), 3.68 (2H, m), 2.76 (1H, m), 1.85 (1H, m), 1.55 (1H, m), 1.36−1.21 (4H, m), 1.03−0.93 (6H, m); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 175.6 (175.2), 168.9, 148.1, 136.0, 132.7, 128.1, 121.7, 115.0, 62.0 (61.9), 51.6 (50.9), 43.8 (43.2), 36.7, 28.3 (28.0), 16.7 (16.4), 14.6 (14.5), 11.8 (11.7); MS (ESI) $m/z$ 338 (M + H$^+$).

**General Procedure for Reduction for the Aryl Nitro Group. Hydrolysis of ester and Cyclization.** To each 900 mg (approximately 0.60 mmol) of the resin bound nitro ester were added 1.78 g (9.4 mmol) of $SnCl_2 \cdot H_2O$ and 5.0 mL of DMF at room temperature. The suspensions were allowed to mix at room temperature overnight. The next day, the supernatants were removed. The resins were washed with DMF, MeOH, $CH_2Cl_2$, and $Et_2O$ and dried in vacuo. From each of the seven resins, 100 mg was removed to analyze the intermediates. To each 800 mg (approximately 0.54 mmol) of the resin-bound aniline ester was added 10 mL of a heterogeneous mixture of 1 N NaOH/THF (1:1). The suspension was slowly heated to 55 °C and allowed to mix at 55 °C overnight. The next day, the supernatants were removed, and the resins were washed with $H_2O$ until the filtrate was neutral. The resins were further washed with DMF, MeOH, $CH_2Cl_2$, and $Et_2O$ and dried in vacuo. From each of the seven resins, 100 mg was removed to analyze the intermediates. To each 700 mg (approximately 0.47 mmol) of the resin bound aniline acid were added 5 mL of DMF, 294 $\mu$L (1.88 mmol) of DIC, and 254 mg (1.88 mmol) of HOBt at room temperature. The suspensions were allowed to mix at room temperature overnight. The next day, the supernatants were removed, and the resins were washed with DMF, MeOH, $CH_2Cl_2$, and $Et_2O$. After the resins were dried, 100 mg from each of the seven resins was removed to analyze the cyclized product. To each 100 mg of the resin was added 1 mL of a solution containing 950 $\mu$L of TFA and 50 $\mu$L of $H_2O$ at ice-bath temperature. The mixtures were slowly warmed to room temperature and allowed to mix for 50 min at room temperature. After 50 min, supernatants were removed, and the resins were washed with MeOH (3 × 2 mL). The combined supernatants were concentrated under a stream of nitrogen, and the concentrated samples were further dried in vacuo. The dried samples were purified by flash chromatography. The products were weighed and analyzed by LC, MS, and $^1$H and $^{13}$C NMR.

**8-Carboxamido-1,5-benzodiazepin-2-one (10a).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 17 mg (88% yield) of a white solid: mp >230 °C; HPLC $t_R$ 1.3 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.43 (2H, m), 6.75 (1H, d, $J$ = 8.9 Hz), 3.62 (2H, t, $J$ = 5.3 Hz), 2.67 (2H, t, $J$ = 5.3 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 176.2, 171.8, 144.4, 125.8, 124.5, 123.9, 123.9, 119.3, 45.2, 37.7; MS (ESI) $m/z$ 206 (M + H$^+$).

**4-Methyl-8-carboxamido-1,5-benzodiazepin-2-one (10b).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 18 mg (76% yield) of a clear oil: HPLC $t_R$ 3.2 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.46 (2H, m), 6.84 (1H, d, $J$ = 8.2 Hz), 3.97 (1H, m), 2.62 (1H, dd, $J$ = 3.2, 13.6 Hz), 2.45 (1H, dd, $J$ = 7.5, 13.6 Hz), 1.32 (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 175.0, 171.8, 144.3, 126.1, 126.1, 124.9, 123.7, 120.3, 53.9, 42.9, 23.7; MS (ESI) $m/z$ 219 (M + H$^+$).

**4-Phenyl-8-carboxamido-1,5-benzodiazepin-2-one (10c).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 16 mg (75% yield) of a white solid: mp >230 °C; HPLC $t_R$ 4.6 min; $^1$H NMR (300 MHz, DMSO) $\delta$ 9.60 (1H, s), 7.67 (1H, s), 7.44−7.24 (6H, m), 7.06 (1H, s), 6.91 (1H, d, $J$ = 8.9 Hz), 6.40 (1H, d, $J$ = 2.9 Hz), 4.97 (1H, m), 2.76−2.50 (2H, m); $^{13}$C NMR (75 MHz, DMSO) $\delta$ 171.9, 169.1, 146.0, 143.8, 130.0, 128.9, 127.9, 127.0, 126.0, 125.6, 124.1, 120.2, 61.5, 44.2; MS (ESI) $m/z$ 282 (M + H$^+$).

**3-Phenyl-8-carboxamido-1,5-benzodiazepin-2-one (10d).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 16 mg (68% yield) of a white solid: mp >230 °C; HPLC $t_R$ 4.6 min; $^1$H NMR (300 MHz, DMSO) $\delta$ 9.64 (1H, s), 7.60 (1H, s), 7.37−7.21 (6H, m), 7.00 (1H, s), 6.66 (1H, d, $J$ = 8.4 Hz), 6.39 (1H, s), 3.99 (1H, d, $J$ = 6.6 Hz), 3.77 (1H, m), 3.57 (1H, m); $^{13}$C NMR (75 MHz, DMSO) $\delta$ 174.4, 169.3, 143.8, 139.9, 130.3, 129.8, 128.4, 125.4, 125.3, 125.0, 124.3, 118.7, 53.0, 50.0; MS (ESI) $m/z$ 282 (M + H$^+$).

**3-(4-Fluorobenzyl)-8-carboxamido-1,5-benzodiazepin-2-one (10e).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 12 mg (55% yield) of a clear oil: HPLC $t_R$ 5.1 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.45 (2H, m), 7.24 (2H, m), 6.98 (2H, t, $J$ = 8.7 Hz), 6.73 (1H, d, $J$ = 8.7 Hz), 3.53−3.30 (2H, m), 3.10−2.95 (2H, m), 2.67 (1H, dd, $J$ = 8.5, 13.5 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 175.4, 170.4, 163.1, 159.9, 143.1, 134.9 (134.9), 130.4, 130.3, 124.4, 122.9, 122.4 (122.4), 117.4, 114.7, 114.4, 56.8, 32.7, 16.9; MS (ESI) $m/z$ 314 (M + H$^+$).

**3-(4-Methoxy)benzyl-8-carboxamido-1,5-benzodiazepin-2-one (10f).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 14 mg (69% yield) of a clear oil: HPLC $t_R$ 4.9 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.42 (2H, m), 7.09 (2H, d, $J$ = 8.5 Hz), 6.76 (2H, d, $J$ = 8.5 Hz), 6.72 (1H, d, $J$ = 8.2 Hz), 3.73 (3H, s), 3.53 (1H, d, $J$ = 2.1, 12.5 Hz), 3.30 (1H, m), 3.05−2.88 (2H, m), 2.60 (1H, dd, $J$ = 8.9, 13.4 Hz); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 177.2, 159.8, 144.7, 132.3, 131.1, 125.8, 123.8, 118.8, 114.9, 58.3, 55.7, 34.1, 18.4; MS (ESI) $m/z$ 326 (M + H$^+$).

**3-Isobutyl-8-carboxamido-1,5-benzodiazepin-2-one (10g).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 13 mg (55% yield) of a clear oil: HPLC $t_R$ 4.5 min; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.42 (2H, m), 6.69 (1H, d, $J$ = 8.3 Hz), 3.50 (2H, m), 2.51 (1H, m), 1.80−1.47 (3H, m), 0.95 (3H, dd, $J$ = 3.7, 6.6 Hz), 0.87 (3H, m); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 176.4 (176.3), 170.5, 142.8, 142.7, 124.0, 122.1, 121.4, 121.4, 121.3, 116.5, 116.4, 53.0 (53.0), 43.1 (42.8), 31.5 (31.0), 27.1 (25.2), 15.7 (14.6), 10.0 (9.5); MS (ESI) $m/z$ 262 (M + H$^+$).

**General Procedure for Alkylation at the N-5 Position of the Benzodiazepinone with Alkyl Halides.** To each 100 mg (approximately 67 $\mu$mol) of the cyclized resins were added 20 equiv (1.34 mmol) of alkyl halides (benzyl bromide, methyl 4-(bromomethyl)benzoate, 1-bromomethyl-3-methoxybenzene, 2-(bromomethyl)naphthalene, 4-nitrobenzyl bromide), 185 mg (1.34 mmol) of $K_2CO_3$, and 1.5 mL of acetone at room temperature. The mixtures were then heated at 55 °C overnight. The next day, the mixtures were cooled to room temperature, and supernatants were separated from the resins. The resins were washed with acetone, $H_2O$, DMF, $CH_2Cl_2$, and $Et_2O$ and then dried in vacuo. To each resin was then added 2 mL of a solution containing 1.9 mL of TFA and 0.1 mL of $H_2O$ at ice-bath temperature. The mixtures were slowly warmed to room temperature and allowed to mix 50 min at room temperature. After 50 min, supernatants were separated, and the resins were washed with MeOH (3 × 2 mL). The combined supernatants were concentrated under a stream of nitrogen. The concentrated samples were further dried in vacuo. The crude products were initially analyzed by LC and MS and then purified by flash chromatography. The purified products were weighed and analyzed by LC, MS and $^1$H and $^{13}$C NMR.

**5-Benzyl-8-carboxamido-1,5-benzodiazepin-2-one (12a).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 17 mg (87% yield) of a white solid: mp 203−205 °C; HPLC $t_R$ 5.12 min; $^1$H NMR (400 MHz, DMSO) $\delta$ 9.60 (1H, s), 7.79−7.04 (10H, m), 4.38 (2H, s), 3.45 (2H, t, $J$ = 6.5 Hz), 2.39 (2H, t, $J$ = 6.5 Hz); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 172.4, 167.2, 144.0, 138.0, 131.8, 128.4, 127.6, 127.1, 126.9, 124.2, 121.8, 119.3, 56.2, 54.8, 33.6; MS (ESI) $m/z$ 296 (M + H$^+$).

For analytical data of **12b−e**, **g−j**, **l−o**, **q−t**, **v−y**, **aa−ad**, **af−ai**, see the Supporting Information.

**4-Methyl-5-benzyl-8-carboxamido-1,5-benzodiazepin-2-one (12f).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 14 mg (68% yield) of a white solid: mp >230 °C; HPLC $t_R$ 5.24 min; $^1$H NMR (400 MHz, DMSO) $\delta$ 9.61 (1H, s), 7.80 (1H, s), 7.51 (1H, dd, $J$ = 2.1, 8.4 Hz), 7.44 (1H, d, $J$ = 2.1 Hz), 7.26−7.09 (7H, m), 4.50−4.35 (2H, AB, $J$ = 15.2 Hz), 3.92 (1H, m), 2.39−2.13 (2H, m), 1.08 (3H, d, $J$ = 6.0 Hz); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 171.8, 167.2, 142.1, 138.4, 133.9, 128.2, 127.9, 127.5, 126.8, 123.8, 122.0, 121.5, 60.0, 56.0, 53.2, 41.1, 16.3; MS (ESI) $m/z$ 310 (M + H$^+$).

**4-Phenyl-5-benzyl-8-carboxamido-1,5-benzodiazepin-2-one (12k).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 16 mg (63% yield) of a white solid: mp >230 °C; HPLC $t_R$ 5.91 min; $^1$H NMR (400 MHz, DMSO) $\delta$ 9.78 (1H, s), 7.84 (1H, s), 7.56−7.15 (13H, m), 7.04 (1H, d, $J$ = 8.3 Hz), 4.91 (1H, dd, $J$ = 4.9, 10.6 Hz), 4.25−4.09 (2H, AB, $J$ = 15.5 Hz), 2.73−2.45 (2H, m); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 170.6, 167.2, 142.7, 141.3, 137.9, 133.2, 128.6, 128.3, 127.8, 127.4, 126.8, 126.6, 124.1, 121.9, 121.8, 68.7, 54.0, 41.4; MS (ESI) $m/z$ 372 (M + H$^+$).

**3-Phenyl-5-benzyl-8-carboxamido-1,5-benzodiazepin-2-one (12p).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 24 mg (97% yield) of a white solid: mp >230 °C; HPLC $t_R$ 6.07 min; $^1$H NMR (400 MHz, DMSO) $\delta$ 9.83 (1H, s), 7.83 (1H, s), 7.59−7.17 (13H, m), 7.08 (1H, d, $J$ = 9.1 Hz), 4.53−4.29 (2H, AB, $J$ = 15.1 Hz), 3.95−3.82 (2H, m), 3.41 (1H, dd, $J$ = 5.2, 10.3 Hz); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 172.3, 167.2, 144.1, 137.9, 136.8, 131.8, 129.4, 128.4, 127.9, 127.6, 127.4, 127.0, 124.3, 122.0, 119.2, 117.4, 61.7, 56.1, 47.5; MS (ESI) $m/z$ 372 (M + H$^+$).

**3-(4-Methoxy)benzyl-5-benzyl-8-carboxamido-1,5-benzodiazepin-2-one (12u).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 19 mg (67% yield) of a white solid: mp 189−191 °C; HPLC $t_R$ 6.27 min; $^1$H NMR (400 MHz, DMSO) $\delta$ 9.65 (1H, s), 7.79 (1H, s), 7.52 (1H, dd, $J$ = 2.0, 8.4 Hz), 7.44 (1H, d, $J$ = 2.0 Hz), 7.29−7.01 (9H, m), 6.76 (2H, d, $J$ = 8.6 Hz), 4.48−4.14 (2H, AB, $J$ = 14.9 Hz), 3.34 (1H, m), 3.22 (1H, dd, $J$ = 5.6, 10.3 Hz), 2.90 (1H, dd, $J$ = 7.1, 13.7 Hz), 2.75 (1H, m), 2.38 (1H, dd, $J$ = 7.1, 13.7 Hz); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 173.5, 167.2, 157.5, 144.5, 137.9, 131.9, 131.5, 129.9, 128.4, 128.2, 127.6, 127.4, 126.9, 126.3, 124.4, 121.9, 119.4, 113.5, 61.3, 56.1, 54.9, 43.0, 32.7; MS (ESI) $m/z$ 416 (M + H$^+$).

**3-(4-Fluoro)benzyl-5-benzyl-8-carboxamido-1,5-benzodiazepin-2-one (12z).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 14 mg (51% yield) of a white solid: mp 189−191 °C; HPLC $t_R$ 6.41 min; $^1$H NMR (400 MHz, DMSO) $\delta$ 9.68 (1H, s), 7.78 (1H, s), 7.53 (1H, dd, $J$ = 2.0, 8.4 Hz), 7.44 (1H, d, $J$ = 2.1 Hz), 7.29−6.95 (11H, m), 4.47−4.17 (2H, AB, $J$ = 14.9 Hz), 3.37 (1H, m), 3.24 (1H, m), 2.94 (1H, dd, $J$ = 7.4, 13.6 Hz), 2.79 (1H, dd, $J$ = 5.9, 12.5 Hz), 2.44 (1H, dd, $J$ = 6.3, 13.6 Hz); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 173.3, 167.2, 144.4, 137.9, 135.8, 135.8, 131.8, 130.8, 130.7, 128.6, 128.1, 127.6, 127.4, 126.9, 124.4, 121.9, 119.4, 117.5, 114.9, 114.7, 61.2, 56.1, 42.8, 32.7; MS (ESI) $m/z$ 404 (M + H$^+$).

**3-Isobutyl-5-benzyl-8-carboxamido-1,5-benzodiazepin-2-one (12ae).** The crude product was purified by flash chromatography ($CHCl_3$/EtOH, 8:1) to obtain 14 mg (59% yield) of a white solid: mp 224−226 °C; HPLC $t_R$ 6.32 min; $^1$H NMR (400 MHz, DMSO) $\delta$ 9.58 (1H, s), 7.80 (1H, s), 7.53 (1H, dd, $J$ = 1.8, 8.4 Hz), 7.46 (1H, d, $J$ = 2.0 Hz), 7.32−7.04 (7H, m), 4.50−4.24 (2H, AB, $J$ = 15.0 Hz), 3.35 (2H, m), 2.34 (1H, dd, $J$ = 7.4, 13.6 Hz), 1.73 (1H, m), 1.35 (1H, m), 0.74 (6H, m); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 174.2 (174.1), 167.2, 144.6, 138.1, 132.0, 128.4, 127.6, 127.4, 126.9, 124.3, 124.2, 121.7, 119.1, 119.1, 59.1 (58.8), 56.5 (56.4), 46.0 (45.8), 32.9 (32.7), 27.5, (24.7), 17.3 (15.1), 11.3 (10.8); MS (ESI) $m/z$ 352 (M + H$^+$).

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**Supporting Information Available:** Analytical data for 28 benzodiazepinones and $^1$H NMR spectra of the 35 benzodiazepinones are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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