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Solid-Phase Synthesis of Tetrahydro-1,4-benzodiazepine-2-one Derivatives as a β-Turn Peptidomimetic Library

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The β-turn has been implicated as an important conformation for biological recognition of peptides or proteins. We adapted the concept of general Cα atom positioning from the cluster analysis and recombination of each ideal β-turn conformation pattern by Garland and Dean (*J. Comput.-Aided Mol. Des.* **1999**, *13*, 469) as one strategy of designing non-peptide β-turn scaffolds. Herein, the Cα positions of tetrahydro-1,4-benzodiazepin-2-one scaffold were analyzed after the calculation of the low-energy conformer using a semiempirical protocol. Three points of corresponding Cα carbons for diverse substitutions in the scaffold were designated, and an efficient solid-phase synthesis of the peptidomimetic library was developed. The scaffold itself was synthesized in solution phase starting from 5-hydroxy-2-nitrobenzaldehyde and loaded to the 4-formyl-3,5-dimethoxyphenoxy (PL-FDMP) resin with high efficiency of reductive amination. Various building blocks for the derivatization of the 7-hydroxyl and N-1 amide nitrogen could be introduced via selective alkylation. Cleavage, parallel column chromatography, and NMR analysis of 62 final compounds confirmed the feasibility of this peptidomimetic library synthesis.

Introduction

Specific conformations of peptides have been known as the key determinates of recognition in a number of signaling processes in biological systems. This includes activation of G-protein coupled receptors (GPCRs) and the catalytic activity of enzymes such as protein kinases and proteases. β-Turn peptides have been implicated as an important conformation for biochemical interactions of peptides or proteins;[1] however, most peptides cannot be used directly as therapeutically useful agents because of their poor bioavailability or pharmacokinetic profiles, and numerous approaches for peptidomimetic drugs have been developed,[2] including non-peptide β-turn secondary structure mimic compounds with conformationally constrained templates.[3,4] In our earlier study,[5] we successfully employed the concept of general Cα atom positioning from the cluster analysis and recombination of each ideal β-turn conformation pattern (Figure 1) published by Garland and Dean[6] in order to design β-turn non-peptide scaffolds, **1**, targeting somatostatin receptors, of which ligands have been well studied as β-turn peptides.[7−9] The biological activity of the somatostatin mimic analogues with the newly designed scaffold, **1**, showed appreciable biological activities in various somatostatin receptor subtypes, providing a validation of the strategy of scaffold design.[5] Thus, a chemical library derived from a β-turn peptide mimic scaffold could be expected to have high potential value in hit discovery as well as the lead discovery processes.

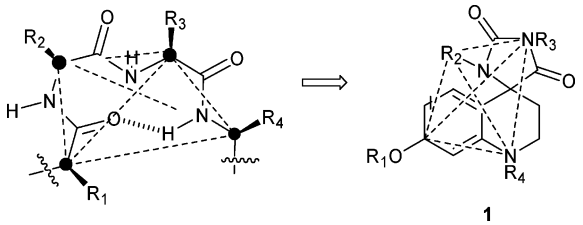

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Figure 1. Schematic representation of the β-turn and Cα carbons.

In this study, we analyzed benzodiazepine skeletons, which have been known as one of the nonpeptide β-turn mimic scaffolds, to apply the concept of general Cα atom positioning and develop a combinatorial synthetic methodology to build a useful peptidomimetic library. Benzodiazepine classes have been an important class of compounds that have displayed selective activities against a diverse array of biological targets,[10,11] which can be explained by their structural features, including a role of peptide β-turn mimic scaffold.[12] Computational analysis using a semiempirical calculation of low-energy conformers of several benzodiazepine classes suggested tetrahydro-1,4-benzodiazepin-2-one scaffold (Figure 2) with the determinations of Cα atom positions, including C-7 of benzene, of which substitution with large or electron donating groups generally shows decreased biological activity in altering the central nervous system,[13] which could be one of the reasons that few such derivatives have been reported. Recently, biologically active benzothiazepines with important residues at the C-7 position

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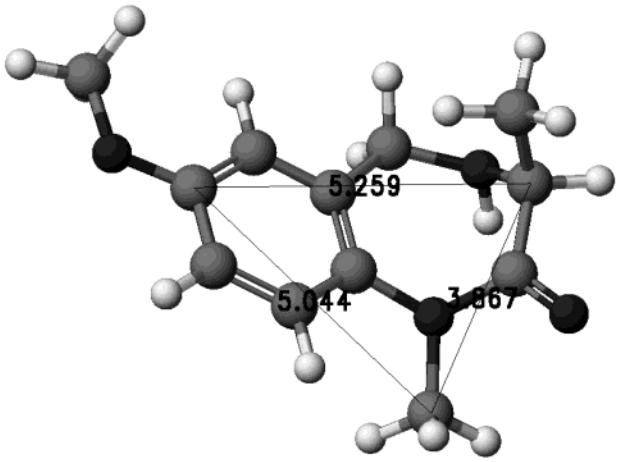


Figure 2. Tetrahydro-1,4-benzodiazepin-2-one scaffold and distance analysis (in Å).

Table 1. Backbone Torsion Angles of the Various Identified Ideal β-Turn Types

	i + 1		*i* + 2	
type	ϕ	ψ	ϕ	ψ
I	−60	−30	−90	0
I′	60	30	90	0
II	−60	120	80	0
II′	60	−120	−80	0
III	−60	−30	−60	−30
III′	60	30	60	30
V	−80	80	80	−80
V′	80	−80	−80	80
VIa	−60	120	−90	0
VIb	−120	120	−60	0
VIII	−60	−30	−120	120

have been reported as tumor necrosis factor α converting enzyme (TACE) inhibitors, showing selective and potent activities against porcine TACE.[14]

Although there have been a number of library syntheses of benzodiazepines since Ellman's group developed a solid-phase synthesis of 1,4-benzodiazepines in the early 1990s,[15] there have been few publications of solid-phase synthesis of tetrahydro-1,4-benzodiazepin-2-ones,[16,17] and most benzodiazepine libraries have limited diversity on the benzene ring, since they use the benzene moiety to link to the resin or they introduced the benzene moiety in building blocks such as anthranilic acids to give diversity.[18] Here, we report a successful parallel solid-phase synthesis of a tetrahydrobenzo[*e*][1,4]diazepin-2-one library with three points of diversity, including the C-7 position, with alkoxy derivatizations, as β-turn peptidomimetics.

Results and Discussion

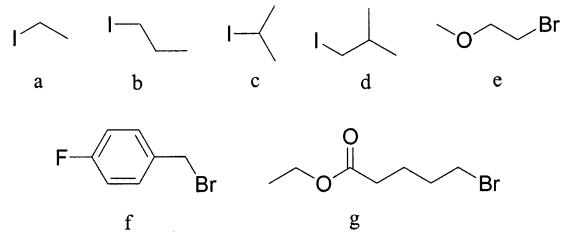
To apply computational methods to search for low-energy conformations of benzodiazepine skeletons, we measured distances of Cα atoms of 11 well-defined ideal β-turn conformations after semiempirical calculations.[19] We built a tetrapeptidal segment with an alanine side chain and introduced constraints of torsion angles (Table 1) along with each β turn type, except for the type VI turn. Type VI required proline in the third position (i + 2) to form a cis peptide bond. Energy minimizations were performed by optimizing the geometry calculation in MOPAC 2002 using the PM3 parameter, and the result showed that most of the distances between the Cα atoms are within the deviation ranges 0.2−0.3 Å, except for the distance between Cα atoms 1 and 4, of which the standard deviation is 0.6 Å (Table 2). On the basis of Cα atom distance analysis, we designed a tetrahydro-1,4-benzodiazepin-2-one scaffold and determined the appropriate positioning of the diversity points. The carbon 7 position of tetrahydro-1,4-benzodiazepin-2-one overlaps with the general distances (3.8 and 5.4 Å) for Cα positioning calculated by Garland and Dean.[6]

Table 2. Distance (in Å) between Cα Atom Pairs after Semiempirical Calculations

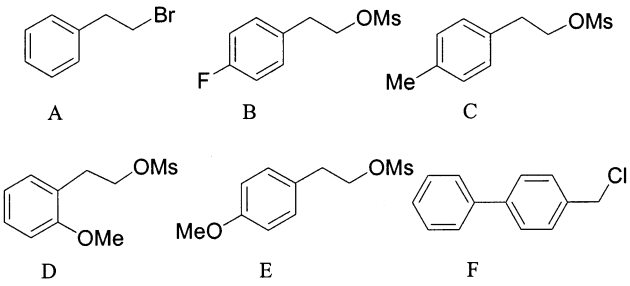
	1−2	1−3	1−4	2−3	2−4	3−4
I	3.90	5.51	5.46	3.97	5.83	3.94
I′	3.93	5.49	5.31	3.96	5.87	3.94
II	3.89	6.22	5.37	3.93	5.83	3.93
II′	3.90	6.13	5.19	3.94	5.81	3.95
III	3.91	5.84	6.55	3.94	5.71	3.94
III′	3.92	5.90	6.67	3.95	5.74	3.93
V	3.90	5.72	6.90	3.93	6.27	3.91
V′	3.92	5.96	6.12	3.95	5.81	3.92
VIa	3.87	5.45	4.93	3.12	5.56	3.94
VIb	3.92	5.47	4.88	3.11	5.15	3.94
VIII	3.89	5.05	5.54	3.91	6.67	3.90
av	3.91	5.70	5.72	3.79	5.84	3.93
dev	0.01	0.29	0.61	0.25	0.24	0.01

Table 3. Building Blocks for the Library Synthesis

Building Blocks for O-alkylation **a-g (R_2)**

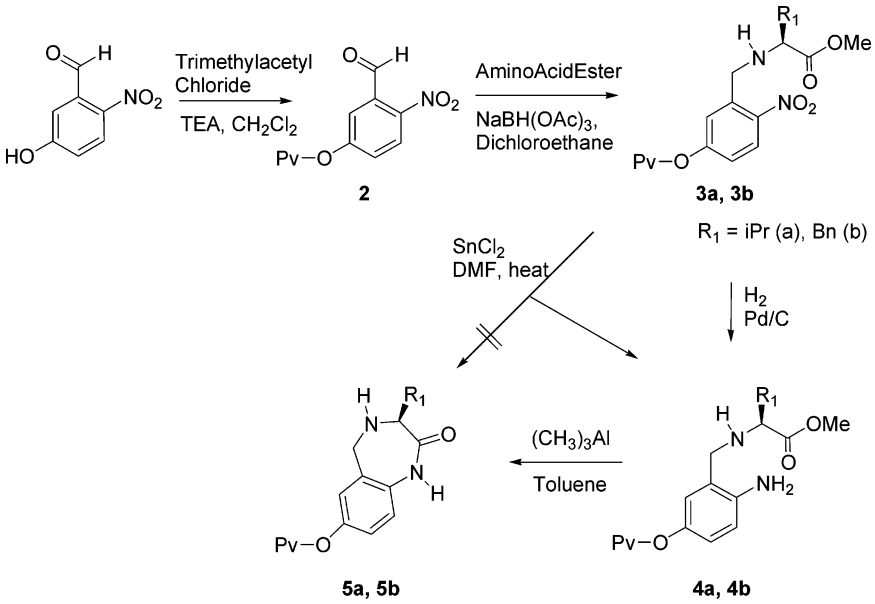


Building Blocks for N-alkylation **A-F (R_3)**

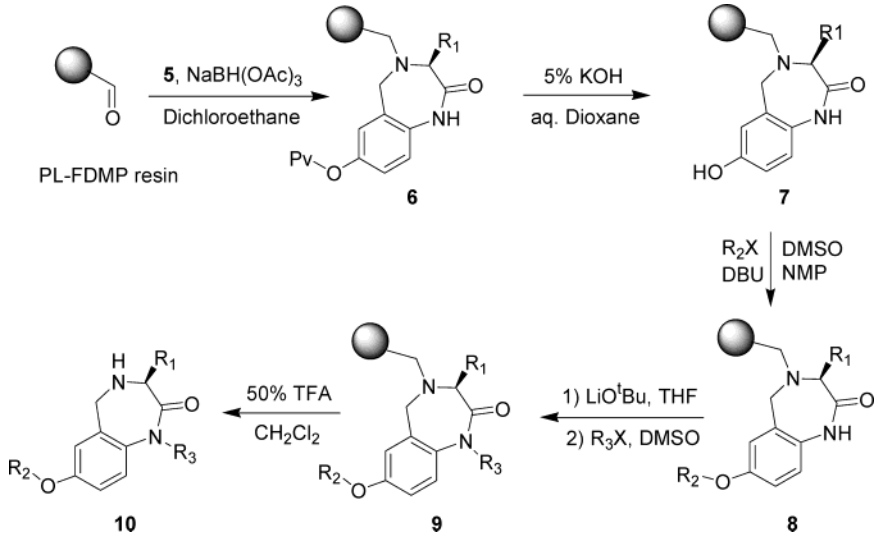


The synthetic strategy for tetrahydro-1,4-benzodiazepin-2-one scaffold is depicted in Scheme 1. Tetrahydro-1,4-benzodiazepin-2-one scaffold with a protected hydroxyl group at carbon 7, **5** was synthesized in solution phase with two different R_1 groups by employing amino acid building blocks. The phenolic functionality of 5-hydroxy-2-nitrobenzaldehyde was first protected with a trimethylacetyl group, then valine methyl ester (R_1 = isopropyl) or phenylalanine methyl ester (R_1 = benzyl) were connected with the aldehyde of **2** through reductive amination reaction using a racemization free protocol[20] to give the secondary amine

Scheme 1. Synthesis of Tetrahydro-1,4-benzodiazepine-2-one Scaffolds.



Scheme 2. Solid Phase Library Synthesis of Tetrahydro-1,4-benzodiazepine-2-one Derivatives.



3 in 70% yield. Attempted reductive cyclization of **3** using $SnCl_2$ was not successful;[21] thus, a two-step procedure involving the reduction of the aryl nitro group under catalytic hydrogenation conditions, followed by intramolecular cyclization with trimethylaluminum, was carried out to afford the tetrahydro-1,4-benzodiazepin-2-one skeletons **5a**,**b**. The overall yield from 5-hydroxy-2-nitro-benzaldehyde was 55% for **5a** and 36% for **5b**.

The resulting 1,4-benzodiazepine-2-one scaffold was loaded onto the 4-formyl-3,5-dimethoxyphenoxy (PL-FDMP) resin by reductive amination in high yield (>95%), even when only 1.5 equiv of the scaffold was used.[22] The loading was calculated by measuring weight increase after drying the loaded resin and was confirmed by IR measurements to detect the disappearance of the aldehyde band of the resin. R_1 and R_2 diversity was introduced in the sequence of derivatizations at the 7-hydroxyl group and was followed by derivatization at the amide nitrogen (N-4 position) since the trimethylacetyl protecting group was unstable under the conditions of the N-alkylations. Thus, the pivaloyl group was hydrolyzed in 3% KOH in dioxane/H_2O (1:1),[23,24] and the resulting resin was distributed to 6 × 4 reaction tubes of a MiniBlock for library synthesis. Various alkyl halides were selected as the building blocks (Table 3) and applied to build up the 7-alkoxy-4-arylalkyl-1,3,4,5-tetrahydro-benzo[*e*][1,4]-diazepin-2-one library. O-alkylation at the C-7 position was carried out with alkylhalides and 1,8-diazabicycl[5.4.0]undec-7-ene (DBU) as a mild base in DMSO/NMP (1:1).[25] The reaction was performed twice at room temperature for 24 h, and the reaction progress for desired products **8** was monitored by TLC after cleavage of a small portion of resin. Alkylations at the N-4 position of the skeleton with various arylalkyl halides were performed using LiO^tBu as a base. Overall, we synthesized 42 (7 × 6) compounds with an isopropyl group at R_1 (7 alkyl halides for O-alkylation and 6 arylalkyl halides for N-alkylation) and 24 (6 × 4) compounds with a benzyl group at R_1. Final compounds were cleaved from the resin, and the crude products were passed through strong anion exchange (SAX) resins to remove trifluoroacetic acid after parallel evaporations. All products

Table 4. Final Yields (%)[a] of 42 Library Compounds with an Isopropyl Group at the R_1 Position

	R_2[b]						
R_3[b]	a	b	c	d	e	f	g
A	36	28	20	0[c]	10	42	35
B	42	43	40	12	16	38	11
C	47	49	36	15	7	49	16
D	36	53	35	3	19	55	0[c]
E	20	46	49	4	32	43	0[c]
F	57	54	61	15	15	44	17

[a] Yields were determined on the basis of the weight of the purified products relative to the initial loading on the PL-FDMP resin (1.5 mmol/g). [b] For the structures of building blocks (R_2 and R_3), see Table 3. [c] Final product was lost during the purification step.

Table 5. Final Yields (%)[a]of 24 Library Compounds with Benzyl Group at R_1 Position

	R_2[b]					
R_3[b]	a	b	c	d	f	g
A	18	44	17	8	30	10
B	25	28	22	5	15	0[c]
C	22	25	30	6	21	2
F	29	31	26	5	13	5

[a] Yields were determined on the basis of the weight of the purified products relative to the initial loading on the PL-FDMP resin (1.5 mmol/g). [b] For the structures of building blocks (R_2 and R_3), see Table 3. [c] Final product was lost during the purification step.

were purified by a parallel silica gel column chromatography system, affording satisfactory yields (Table 4, Table 5). ^{1}H NMR spectra of all the products were recorded to confirm the structures.

Conclusion

In summary, the distance analysis of Cα atoms was performed to design a scaffold that mimics a peptide β-turn. The C-7 and N-4 positions of the 1,4-benzodiazepins were detected as the Cα atom sites for building up chemical diversity. A solid-phase synthetic strategy of 7-alkoxy-4-arylalkyl-1,3,4,5-tetrahydro-benzo[*e*][1,4]diazepin-2-ones has been established and validated through preparing 62 library members. Therefore, further diverse β-turn peptidomimetic library compounds can be generated by either substituting the R_1 group with various amino acids or adding more building blocks for R_2 and R_3 groups. In addition, the focused or targeted libraries, which employ the results in this study, would be useful to discover new lead compounds acting at various protein targets, of which natural ligands are peptides or proteins with β-turn conformations.

Experimental Section

General Procedures. Starting materials, reagents, and solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as supplied without further purification. PL-FDMP resin was purchased from Polymer Laboratories. ^{1}H NMR spectra were recorded on Bruker Avance 600 MHz and JEOL 300 MHz; chemical shifts (δ) are reported in ppm relative to TMS as the internal standard. All samples were dissolved in $CDCl_3$ unless otherwise specified. LC/MS data were recorded on VG BIOTECH platform. Parallel solid-phase synthesis was performed on a MiniBlock from Mettler-Toledo Bohdan, Inc. (Vernon Hills, IL). The SPE tube, SAX was purchased from Alltech Associates (Lot No. 2312; Deerfield, IL). Parallel purification was performed on Quad3, Parallel FLASH Purification System, Biotage, Inc. (Charlottesvile, VA). Four building blocks for N-alkylation were prepared by mesylation of 4-fluoro, 4-methyl, 4-methoxy, and 2-methoxy phenethyl alcohols. The general condition for mesylation was mixing starting compound with methansulfonyl chloride and TEA in CH_2Cl_2 at 0 °C. They were purified by simple work-up (aq NH_4Cl/EtOAc).

2,2-Dimethylpropionic Acid 3-Formyl-4-nitrophenyl Ester (2). To 5-hydroxy-2-nitro-benzaldehyde (9.07 g, 54.26 mmol) in CH_2Cl_2 (150 mL) was added trimethylacetyl chloride (7.34 mL, 59.66 mmol), stirring at 0 °C. After a dropwise addition of Et_3N (7.56 mL, 54.26 mmol), the mixture was stirred at room temperature for 30 min. The reaction mixture was then partitioned between saturated NH_4Cl solution and $CHCl_3$. The organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography ($CHCl_3$/MeOH = 100/1) giving 13.56 g of **2** (yield 99.5%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.44 (s, 1H), 8.10 (d, J = 12 Hz, 1H), 7.25 (s, 1H), 7.07 (d, J = 12 Hz, 1H), 1.336 (s, 9H). MS (ESI) *m*/*z*: 252.1 ($[M + H]^+$).

2-[5-(2,2-Dimethylpropionyloxy)-2-nitrobenzylamino]-3-methylbutyric Acid Methyl Ester (3a) 2 (5 g, 20 mmol) and $NaBH(OAc)_3$ (5.51 g, 26 mmol) were dissolved in dichloroethane/DMF (70 mL/30 mL). L-Valine methyl ester hydrochloride (4.03 g, 24 mmol) was added to the mixture and then stirred for 1 h at room temperature. The residue obtained was extracted with chloroform and washed well with saturated $NaHCO_3$. The product was purified by silica gel column chromatography, eluting with hexane/EtOAc/MeOH (30/1/1) to afford 4.85 g of **3a** (yield 66.2%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 9 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 2.4 Hz, 9 Hz, 1H), 4.03 (ABq, J = 15.6 Hz, 117.9 Hz, 2H), 3.71 (s, 3H), 3.0 (d, J = 6.2 Hz, 1H), 1.95−1.91 (m, 1H), 1.37 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H). MS (ESI) *m*/*z*: 305.1 ($[M + H]^+$).

2-[5-(2,2-Dimethylpropionyloxy)-2-nitrobenzylamino]-3-phenylpropionic Acid Methyl Ester (3b). Using the same procedure as for the preparation of **3a**, from phenylalanine methyl ester hydrochloride, 9.82 g of **3b** was obtained (yield 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.00 (d, J = 9 Hz, 1H), 7.3−7.0 (m, 7H), 4.03 (ABq, J = 15.6 Hz, 53.4 Hz, 2H), 3.66 (s, 3H), 3.53 (t, J = 7.2 Hz, 1H), 3.00−2.92 (m, 2H), 1.37 (s, 9H). MS (ESI) *m*/*z*: 415.2 ($[M + H]^+$).

2-[2-Amino-5-(2,2-dimethylpropionyloxy)benzylamino]-3-methylbutyric Acid Methyl Ester (4a). 3a (4.80 g, 13.1 mmol) was dissolved in methanol (30 mL) and hydrogenated under 1 atm of H_2 atmosphere over 10% Pd/C (0.75 g) at room temperature for 4 h. The reaction mixture was filtered through a Celite bed and washed with methanol. After the evaporation of methanol, the product was purified by silica gel column chromatography and eluted with hexane/EtOAc

(3/1) to afford 4.15 g of **4a** (yield 94.8%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.78 (dd, J = 2.6 Hz, 8.5 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 4.15 (bs, 2H, NH_2), 3.76 (s, 3H), 3.65 (ABq, J = 12.3 Hz, 139 Hz, 2H), 3.05 (d, J = 5.8 Hz, 1H), 1.97−1.89 (m, 1H), 1.36 (s, 9H), 0.93 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H). MS (ESI) m/z: 367.1 ([M + H]$^+$).

2-[2-Amino-5-(2,2-dimethylpropionyloxy)benzylamino]-3-phenylpropionic Acid Methyl Ester (4b). Following the procedure as outlined for the preparation of **4a**, 6.71 g (yield 73%) of **4b** was synthesized from **3b** (9.81 g, 23.69 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.30−7.12 (m, 5H), 6.76 (dd, J = 2.7 Hz, 8.4 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H), 3.62 (ABq, J = 12.3 Hz, 76.8 Hz, 2H), 3.51 (t, J = 9 Hz, 1H), 3.04 (dd, J = 5.4 Hz, 13.5 Hz, 1H), 2.79 (dd, J = 9 Hz, 13.5 Hz, 1H), 1.31 (s, 9H). MS (ESI) m/z: 385.1 ([M + H]$^+$).

2,2-Dimethylpropionic Acid 3-Isopropyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-7-yl Ester (5a). Compound **4a** (4.14 g, 12.3 mmol) was dissolved in toluene (30 mL), and the reaction flask was placed in an ice bath. $AlMe_3$ (2 M) in toluene (24 mL) was added dropwise for 5 min with stirring. After an additional 10 min stirring at 0 °C, the temperature was slowly increased to room temperature. After 90 min of stirring, the reaction was quenched with 30 mL of MeOH at 0 °C. (A white precipitate was observed.) The mixture was warmed to room temperature and stirred for 10 min and partitioned between saturated $NaHCO_3$ and EtOAc. Before separating the organic layer, the mixture was filtered. Then the biphasic filtrate was separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 40/1) to afford 3.3 g of **5a** (yield 88.2%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.41 (s, 1H), 6.99−6.94 (m, 3H), 3.98 (ABq, J = 13.5 Hz, 95.4 Hz, 2H), 3.18 (d, J = 7.3 Hz, 1H), 2.21−2.17 (m, 1H), 1.35 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H). MS (ESI) m/z: 337.1 ([M + H]$^+$).

2,2-Dimethylpropionic Acid 3-Benzyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-7-yl Ester (5b). Following the same procedure as outlined in the preparation of **5a**, 6.71 g (yield 64.4%) of **5b** was prepared from **4b** (6.71 g, 17.4 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.97 (s, 1H), 7.26−7.19 (m, 5H), 6.97−6.90 (m, 3H), 3.94 (ABq, J = 13.8 Hz, 76.5 Hz, 2H), 3.70 (dd, J = 5.7 Hz, 7.8 Hz, 1H), 3.22 (dd, J = 5.7 Hz, 13.8 Hz, 1H), 2.92 (dd, J = 7.8 Hz, 13.8 Hz, 1H), 1.34 (s, 9H). MS (ESI) m/z: 353.1 ([M + H]$^+$).

General Procedure of Reductive Amination for the Preparation of Resin-Bound Benzodiazepine (6). To the PL-FDMP resin (1.5 mmol/g, 2.7 g, 4.05 mmol) was added a solution of **5a** (2.3 g, 7.55 mmol) and $NaBH(OAc)_3$ (1.73 g, 8.1 mmol) in 1,2-dichloroethane (100 mL). The mixture was gently stirred for 1 h at room temperature and filtered, and the resin was sequentially washed with DMF (3 × 30 mL), CH_2Cl_2 (3 × 30 mL), and MeOH (3 × 20 mL). The resin was dried in vacuo to a constant weight (yield 94.8%).

Hydrolysis of Pivaloyl Group of the Resin-Bound Benzodiazepine-2-one Scaffold (7). Resin-bound benzodiazepine-2-one scaffold, **6** (3.91 g for R_1 = isopropyl, 4.29 g for R_2 = benzyl) was shaken in 3% KOH solution in dioxane/water (50 mL:50 mL) for 24 h at room temperature. The mixture was filtered, and the resin was sequentially washed with DMF (3 × 25 mL), CH_2Cl_2 (3 × 25 mL), and MeOH (2 × 20 mL). The resin was dried in vacuo to a constant weight and ready for combinatorial library synthesis.

General Procedure of O-Alkylation (8). Resin-bound benzodiazepine-2-one, **7**, was distributed in each reaction tube in a MiniBlock, (150 mg, 0.168 mmol each) and suspended in 1:1 DMSO/NMP (4 mL). Alkyl halides (0.84 mmol) and DBU (126 μL, 0.84 mmol) were added to each reaction tube. The reaction mixtures were shaken for 24 h, the mixture was filtered, and the resin was washed with DMF and CH_2Cl_2 three times. The reaction was repeated once more, and the final washing step was finished with THF for the next N-alkylation step.

General Procedure of N-Alkylation (9). Each resin-bound O-alkylated benzodiazepine-2-one (0.168 mmol), **8**, was suspended in THF (3 mL). Lithium-*tert*-butoxide (1 M, 840 μL, 0.84 mmol) in THF was added to each reaction tube. After shaking the reaction tube for 1 h, the THF solution was removed by filtration, and the resin was treated with alkyl halide (0.84 mmol) in 4 mL of DMSO and shaken for 12 h. The mixture was filtered, and the resin was sequentially washed with DMF (3 × 4 mL), CH_2Cl_2 (3 × 4 mL), and MeOH (2 × 4 mL). The procedure was repeated once more.

General Procedure of Cleavage and Purification (10). Each resin was treated with 50% TFA/CH_2Cl_2 (3 mL) for 2 h, and the resin was filtered and washed well with CH_2Cl_2. The cleavage step was repeated twice. The combined filtrate was evaporated in parallel under reduced pressure using a Genevac DD-4 system, and the products were dissolved in chloroform and eluted through SAX resin to convert the free base form. The eluent was evaporated, and all final products were purified by a Quad3 parallel purification system with an appropriate mixture of hexane/EtOAc. Homogeneous fractions were combined and evaporated in vacuo, and the weight of residue was determined to calculate the yield. The structures of all final products were determined by ^{1}H NMR. The spectral data of selected compounds are shown.

7-Ethoxy-3-isopropyl-1-phenethyl-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10aaA). (R_1 = isopropyl, R_2 = ethyl, R_3 = phenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.28−7.12 (m, 5H), 6.96 (d, J = 8.7 Hz, 1H), 6.87 (dd, J = 2.7 Hz, 8.9 Hz, 1H), 6.81 (d, J = 2.7 Hz, 1H), 4.33−4.26 (m, 1H), 4.04 (q, J = 6.9 Hz, 2H), 3.84−3.76 (m, 1H), 3.72 (ABq, J = 12 Hz, 30.9 Hz, 2H), 3.07−3.02 (m, 1H), 2.83 (d, J = 9.3 Hz, 1H), 2.79−2.71 (m, 1H), 1.43 (t, J = 6.9 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H).

1-[2-(4-Fluorophenyl)ethyl]-3-isopropyl-7-propoxy-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10abB). (R_1 = isopropyl, R_2 = propyl, R_3 = 4-fluoro phenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.14−7.10 (m, 2H), 6.99−6.81 (m, 5H), 4.35−4.25 (m, 1H), 3.93 (t, J = 6.6 Hz, 2H), 3.85−3.75 (m, 1H), 3.70 (ABq, J = 12 Hz, 27.3 Hz, 2H), 3.07−2.95 (m, 1H), 2.81 (d, J = 9.3 Hz, 1H), 2.80−2.68 (m, 1H), 2.15−2.04 (m, 1H), 1.82 (qt, J = 6.7 Hz, 7.3 Hz, 2H), 1.05

(t, J = 7.5 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H).

7-Isopropoxy-3-isopropyl-1-(2-*p*-tolylethyl)-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10acC). (R_1 = isopropyl, R_2 = isopropyl, R_3 = 4-methyl phenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.06 (s, 4H), 6.97 (d, J = 8.7 Hz, 1H), 6.85 (dd, J = 2.7 Hz, 8.7 Hz, 1H), 6.80 (d, J = 2.7 Hz, 1H), 4.60−4.50 (m, 1H), 4.33−4.24 (m, 1H), 3.80−3.69 (m, 1H), 3.73 (ABq, J = 12.6 Hz, 34.2 Hz, 2H), 3.07−2.94 (m, 1H), 2.85 (d, J = 9.3 Hz, 1H), 2.79−2.66 (m, 1H), 2.30 (s, 3H), 2.19−2.06 (m, 1H), 1.37 (d, J = 2.4 Hz, 3H), 1.34 (d, J = 2.1 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H).

7-Isobutoxy-3-isopropyl-1-(2-*p*-tolylethyl)-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10adC). (R_1 = isopropyl, R_2 = 2-methyl propyl, R_3 = 4-methyl phenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.06 (s, 4H), 6.97 (d, J = 8.7 Hz, 1H), 6.86 (dd, J = 2.7 Hz, 8.7 Hz, 1H), 6.81 (d, J = 2.7 Hz, 1H), 4.32−4.20 (m, 1H), 3.80−3.60 (m, 5H), 3.10−2.90 (m, 1H), 2.82 (d, J = 9.3 Hz, 1H), 2.75−2.65 (m, 1H), 2.30 (s, 3H), 2.15−2.00 (m, 2H), 1.03 (d, J = 6.9 Hz, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H).

3-Isopropyl-7-(2-methoxyethoxy)-1-[2-(4-methoxyphenyl)-ethyl]-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10aeE). (R_1 = isopropyl, R_2 = 2-methoxyethyl, R_3 = 4-methoxyphenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.08−6.78 (m, 7H), 4.34−4.24 (m, 1H), 4.15−4.09 (m, 2H), 3.77 (s, 3H), 3.76−3.65 (m, 5H), 3.46 (s, 3H), 3.00−2.97 (m, 1H), 2.83 (d, J = 9.3 Hz, 1H), 2.75−2.65 (m, 1H), 2.17−2.10 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H).

5-(1-Biphenyl-4-ylmethyl-3-isopropyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-7-yloxy)pentanoic Acid Ethyl Ester (10agF). (R_1 = isopropyl, R_2 = $CH_2CH_2CH_2$-$CH_2COOC_2H_5$, R_3 = 4-phenyl benzyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.56−7.29 (m, 9H), 7.16 (d, J = 8.7 Hz, 1H), 6.86 (dd, J = 2.7 Hz, 8.7 Hz, 1H), 6.77 (d, J = 2.7 Hz, 1H), 5.11 (ABq, J = 24.3 Hz, 39 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.00−3.95 (m, 2H), 3.64 (ABq, J = 12 Hz, 28.2 Hz, 2H), 2.92 (d, J = 9.7 Hz, 1H), 2.39−2.35 (m, 2H), 2.20−2.10 (m, 1H), 1.85−1.78 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

7-(4-Fluorobenzyloxy)-3-isopropyl-1-[2-(2-methoxyphenyl)-ethyl]-1,3,4,5-tetrahydrobenzo[*e*][1,4] diazepin-2-one (10afD). (R_1 = isopropyl, R_2 = 4-fluorobenzyl, R_3 = 2-methoxyphenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.43−7.39 (m, 2H), 7.20−7.06 (m, 3H), 7.02−6.89 (m, 3H), 6.77−6.71 (m, 3H), 5.03 (s, 2H), 4.33−4.20 (m, 1H), 3.80−3.70 (m, 1H), 3.76 (s, 3H), 3.72 (ABq, J = 12 Hz, 27.6 Hz, 2H), 3.06−2.90 (m, 1H), 2.83 (d, J = 9.3 Hz, 1H), 2.76−2.65 (m, 1H), 2.19−2.02 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H).

3-Benzyl-7-propoxy-1-(2-*p*-tolylethyl)-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10bbC). (R_1 = benzyl, R_2 = propyl, R_3 = 4-methyl phenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26−7.16 (m, 5H), 7.05−6.88 (m, 5H), 6.82 (dd, J = 2.7 Hz, 8.7 Hz, 1H), 6.73 (d, J = 2.7 Hz, 1H), 4.40−4.30 (m, 1H), 3.90 (t, J = 6.3 Hz, 2H), 3.75−3.65 (m, 1H), 3.69 (ABq, J = 15.9 Hz, 48.9 Hz, 2H), 3.48 (t, J = 6.6 Hz, 1H), 3.18 (dd, J = 6.9 Hz, 13.5 Hz, 1H), 3.00−2.90 (m, 1H), 2.85 (dd, J = 6.9 Hz, 13.8 Hz, 1H), 2.72−2.65 (m, 1H), 2.29 (s, 3H), 1.80 (tq, J = 6.9 Hz, 7.2 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H).

3-Benzyl-1-biphenyl-4-ylmethyl-7-isobutoxy-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10bdF). (R_1 = benzyl, R_2 = 2-methyl propyl, R_3 = 4-phenyl benzyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.55−7.17 (m, 14H), 7.12 (d, J = 8.7 Hz, 1H), 6.84 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 6.71 (d, J = 2.7 Hz, 1H), 5.03 (ABq, J = 15 Hz, 77.4 Hz, 2H), 3.75−3.53 (m, 5H), 3.21 (dd, J = 6.6 Hz, 13.2 Hz, 1H), 2.87 (dd, J = 6.8 Hz, 13.8 Hz, 1H), 2.02−2.08 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H).

3-Benzyl-7-(4-fluorobenzyloxy)-1-[2-(4-fluorophenyl)-ethyl]-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one (10bfB). (R_1 = benzyl, R_2 = 4-fluorobenzyl, R_3 = 4-fluorophenethyl) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41−6.81 (m, 16H), 5.00 (s, 2H), 4.37−4.34 (m, 1H), 3.78−3.73 (m, 1H), 3.67 (ABq, J = 12.9 Hz, 31.8 Hz, 2H), 3.66−3.52 (m, 1H), 3.48 (t, J = 6.9 Hz, 1H), 3.20 (dd, J = 7.2 Hz, 13.8 Hz, 1H), 3.02−2.90 (m, 1H), 2.87 (dd, J = 6.6 Hz, 13.8 Hz, 1H), 2.78−2.69 (m, 1H).

Semiempirical Calculations. Computational analysis was performed using the CAChe program (BioMedCAChe Version 5.0, CAChe Scientific, Inc.). The structures of each type of β-turn peptide and the benzodiazepine scaffold was subjected to calculation to search the lowest energy conformer with comparisons of HF (heat of formation) by performing an optimized geometry calculation in MOPAC 2002 using PM3 parameters.

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