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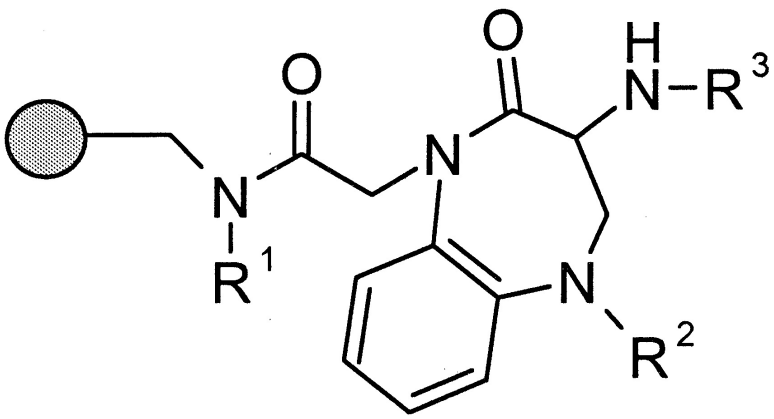

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Synthesis of a 10 000 Member 1,5-Benzodiazepine-2-one Library by the Directed Sorting Method

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The solid-phase synthesis of a 10 000 member combinatorial library of 1,5-benzodiazepine-2-one derivatives is reported. The 3-amino-1,5-benzodiazepine-2-one scaffold was prepared in solution, and the benzamide nitrogen was used as a point of attachment to the resin. The 5-aniline and 3-amine were then used as points of diversity. A 10 000 member library was synthesized using the Irori directed sorting system, and after analysis of a representative sample from the library, the Irori system was used to remove the compounds of lower purity.

Introduction

Over a decade ago, the concept of "privileged scaffold"[1] was introduced, based on the observation that some molecular frameworks have an exceptional ability to mimic peptide ligands. Compounds from the same class can mimic natural ligands that have little in common, and small changes in their substituents result in compounds with a high affinity for different receptors. The most representative of these "privileged scaffolds" is probably the benzodiazepine scaffold (Figure 1). Compounds **1**, **2**, and **3** bind with high affinity to three different receptors with very different endogenous ligands.[1−3] Although there is no proof that they bind in the same region of the receptor as the endogenous ligand, these compounds seemed to have common features which facilitate binding to proteinaceous receptor surfaces. Quite naturally these "privileged scaffolds" have been prime targets for the synthesis of lead generation libraries.[4] Benzodiazepine derivatives have been some of the first small molecules synthesized on solid phase, and many combinatorial approaches have been reported.[5−7] The main synthetic interest, however, has so far focused on 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones, with 1,5-benzodiazepin-2-ones receiving much less attention. The 1,5-benzodiazepine-2-one core is also a "privileged scaffold" found in compounds active against a variety of target types (protease inhibitors, 7-TM receptors; examples are given in Figure 1).[8−10] A single solid-phase approach to 1,5-benzodiazepin-2-one derivatives has been reported by two groups,[7] using 4-fluoro-3-nitrobenzoic acid as starting material and a carboxamide at position 8 as a point of attachment to the resin. We report here an alternative approach which involves the synthesis of the protected 3-amino-1,5-benzodiazepin-2-one scaffold in solution, attachment to the resin through the 1-amide nitrogen, and its subsequent functionalization. We also describe the synthesis and characterization of a 10 000 member library with this chemistry using the Irori directed sorting method.

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Results and Discussion

Our synthetic strategy is outlined in Scheme 1. The central 3-amino-1,5-benzodiazepin-2-one scaffold was prepared by solution-phase chemistry and attached to the resin through the benzamide nitrogen. A phthalimide protecting group was chosen for the 3-amino group because (1) it was compatible with an acid cleavable linker, (2) it left a single base labile amide proton in the molecule, and (3) it allowed an easy purification of the scaffold by filtration. 3-*N*-Boc-1,5-benzodiazepin-2-one was prepared from α-Boc-diamino propionic acid according to the published procedure,[9b] and the Boc group was then replaced by a phthalimide group using a standard procedure.

The attachment of the scaffold to the resin and its fuctionalization is described in Scheme 2. The first combinatorial step was the attachment of primary amines onto the dimethoxy-benzaldehyde (BAL) linker through reductive amination.[6a,11] The amine was then cleanly reacted with bromoacetic acid and DIC. Treatment of the benzodiazepine scaffold **9** with potassium *tert*-butoxide generated the benzamide anion which was quenched with the resin bound bromide. Only 2 equiv of the scaffold was needed for a complete conversion of the bromide, and the reaction was found to require strictly anhydrous conditions as traces amount of water produced the hydroxyacetamide as a byproduct. Functionalization of the 5-amine required strong conditions. Alkylation with benzylic chlorides or bromides required high concentration (0.6 M solution) in DMF at 80 °C and potassium iodide. Acylation with acyl halides and sulfonyl chlorides proceeded at high concentration in neat pyridine at 80 °C with a catalytic amount of DMAP, and reaction with isocyanates proceeded in toluene at 40 °C. After removal of the phthalimide protecting group at 50 °C in 25% hydrazine in 2-propanol, the primary amine was reacted with carboxylic acids and sulfonyl chlorides. Acylation was found to proceed cleanly with EDC, but for less reactive carboxylic acids, HBTU was preferred. Sulfonylation was found to proceed cleanly in DCM-pyridine and DCM-triethylamine,

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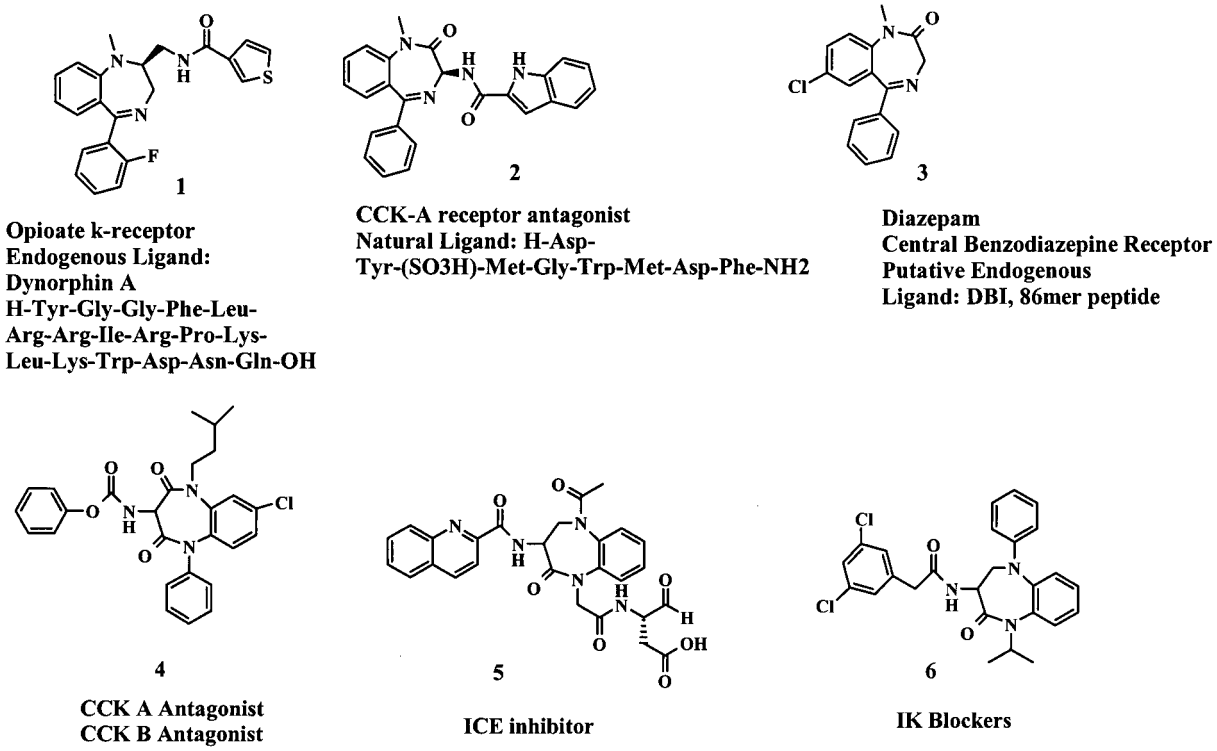
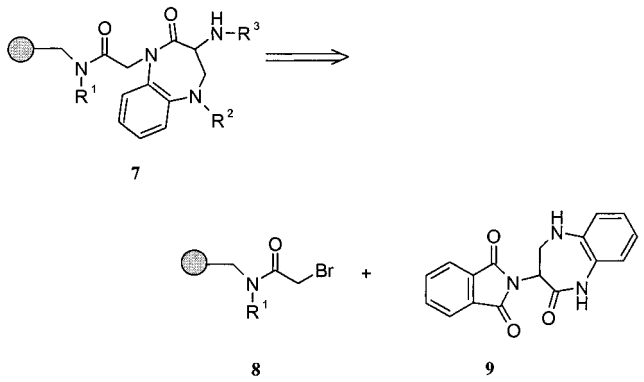


Figure 1. Examples of active benzodiazepine derivatives.

Scheme 1. Library Strategy



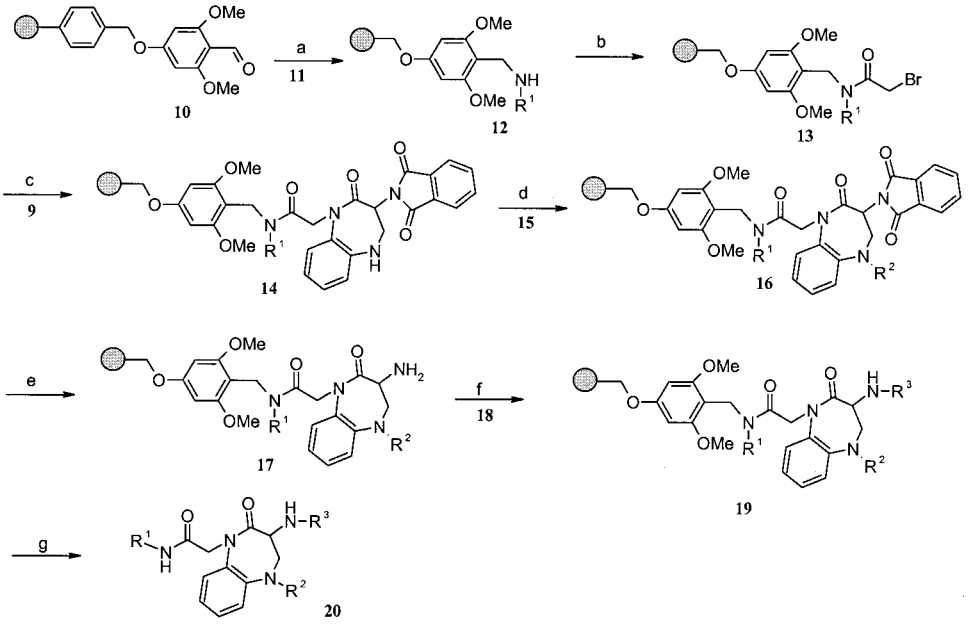
but the latter conditions allowed selective reaction on the primary amine when the 5-amine was left unreacted.

The scope and limitation of this synthetic route was investigated (Tables 1−4). Few functional groups were tolerated at R1 because of the strong alkylation conditions at the 5-amine and the reaction with a strong nucleophile such as hydrazine. At the second combinatorial position, aliphatic halides and benzoyl chloride were not reactive enough, but aliphatic acid chlorides and sulfonyl chlorides gave a complete reaction. Several functional groups were tolerated at R3: carboxylic acids containing functional groups such as alcohol, phenol, benzotriazole, tertiary amine, Boc-protected amine, *tert*-butyl ether, and imidazole gave clean a reaction. The chemistry was validated by the preparation and characterization of 20 compounds (Table 1). The yields were good for all 20 compounds, and the purity measured by HLPC (ELS and UV detector) and ^{1}H NMR was excellent.

This chemistry was applied to the synthesis of a 10 530 member library. To maximize the diversity of the library, clustering tools were used. Lists of commercially available amines, sulfonyl chlorides, carboxylic acids, acid chlorides, and isocyanates were subjected to Ward's clustering using Daylight 2D fingerprints;[12] cluster centroids having 75% or greater similarity to the original set were discarded with the remaining centroids (or similar replacement, based on cost, availability, and other factors) used to form the candidate lists. Reagents for the library were then chosen from these lists to maximize diversity within compatibility of the chemistry.

The library was produced as a full 18 × 13 × 45 array, using the Irori system and the reagents listed in Figures 2−4. Only 17, 12, and 44 reagents were used at each position, because "no substitution" was included at the three diversity steps. For the first combinatorial position, unsubstituted primary amides were obtained using Rink amide resin. Analysis of a random sample of the library was used to assess its overall purity. The library being constructed as a combination of a small number of reagents, a small random selection could be statistically significant. In the set of 526 compounds (5% of the total) randomly chosen, every reagent used was present in at least 5 compounds analyzed, and for the most of them in 8 to 20 compounds analyzed. Average purity per reagent was calculated by averaging the purity of all compounds analyzed containing this reagent and was used as an indicator of how well the reagent performed in the synthesis. The set of 526 compounds was cleaved and analyzed by HPLC with a combination of mass spectrometry (MS) and evaporative light scattering (ELS) detection. The MS detector was used to confirm the identity of the compounds, and purity was based on ELS detection. The overall purity distribution of the analyzed set is depicted in Figure 5a. Four of the alkylating reagents used at R2 **15**{*9*−*12*}were found to have extremely low average purity, and

Scheme 2[a]



[a] Reagents and conditions: (a) R^1NH_2, $NaBH(OAc)_3$, DMF, 1% AcOH, rt, 12 h; (b) Br-CH_2-CO_2H, DIC, DCM, rt, 12 h; (c) **9**, KOtBu, DMF, rt, 12 h; (d) RCH_2-Br, KI, DIEA, DMF, 80 °C, 12 h or RCOCl, pyridine, DMAP (cat.) 80 °C, 12 h or RSO_2Cl, pyridine, DMAP (cat.) 50 °C, 12 h or RNCO, toluene, 40 °C, 12 h; (e) 25% hydrazine in 2-propanol, 50 °C, 3 h; (f) RCO_2H, EDC, DMF, rt, 12 h or RCO_2H, HBTU, DIEA, DMF, rt, 12 h or RSO_2Cl, DCM, Et_3N, rt, 12 h; (g) 50% TFA-DCM, rt, 1 h.

Table 1. Validation Set

entry	R3	yield[a]	ELS purity	UV purity
1	**20**{*3,1,5*}	64	96	74
2	**20**{*1,2,1*}	49	99	84
3	**20**{*2,1,2*}	78	93	66
4	**20**{*4,1,4*}	81	93	76
5	**20**{*2,1,4*}	82	91	55
6	**20**{*4,1,1*}	72	97	70
7	**20**{*2,1,3*}	71	93	60
8	**20**{*1,4,1*}	63	82	60
9	**20**{*4,1,3*}	79	92	60
10	**20**{*3,1,3*}	83	95	74
11	**20**{*4,1,5*}	80	92	64
12	**20**{*3,1,1*}	71	91	63
13	**20**{*1,3,1*}	39	96	68
14	**20**{*3,1,2*}	75	96	60
15	**20**{*1,1,3*}	83	89	70
16	**20**{*2,1,5*}	75	94	70
17	**20**{*1,1,1*}	63	99	87
18	**20**{*4,1,2*}	91	97	70
19	**20**{*2,1,1*}	63	97	57
20	**20**{*1,1,5*}	81	93	75

[a] Yield based on recovered material of indicated purity.

on observation of the wells, it was found that nothing had been cleaved from the resin. A possible explanation is that premature cleavage from the resin occurred during the alkylation step with those reagents. This was not a general rule as compounds alkylated with 4-trifluoromethyl-benzyl chloride **15**{*3*} and *tert*-butyl bromoacetate **15**{*5*} were produced in good yield and good purity.

Because only 5% of the library compounds had been cleaved to be analyzed and the remainder of the library had been left in MicroKans, we were able to use the Irori equipment to remove all the compounds affected by this premature cleavage. The Irori Autosort was used to sort the library according to step 2, and the MicroKans which had been exposed to reagents **15**{*9*−*12*} at R2 were removed.

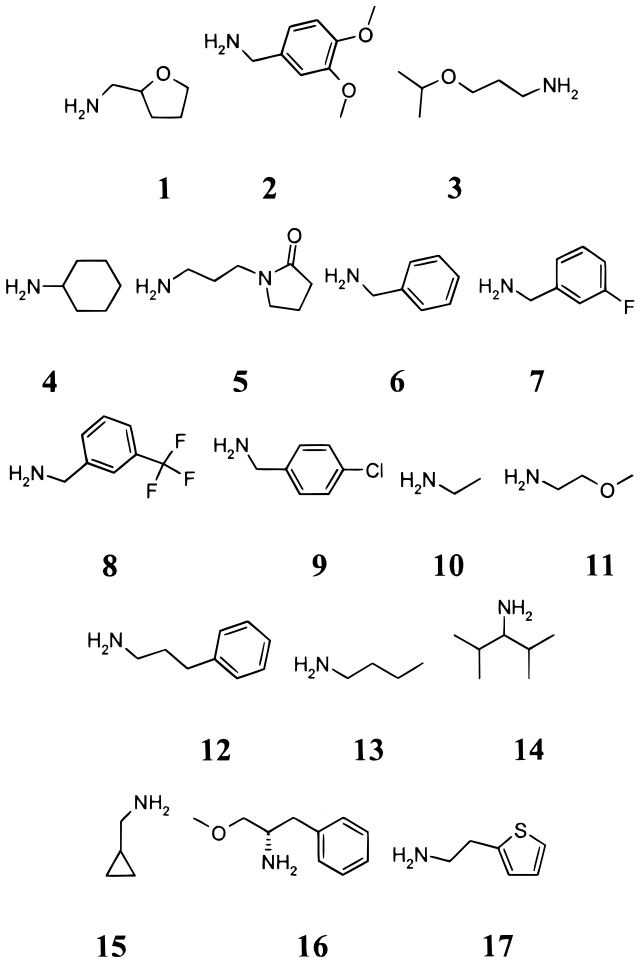


Figure 2. Diversity reagents **11**{*1*−*17*}.

The rest of the library was cleaved to afford a 7149 member library with an excellent purity distribution (Figure 5b). More

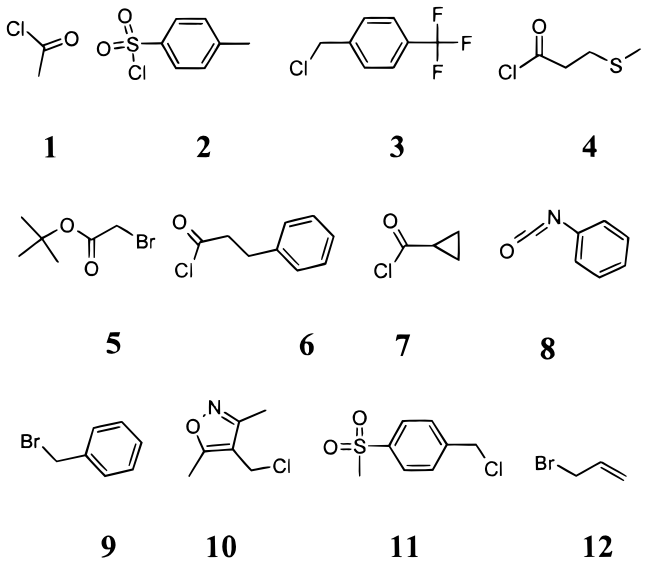


Figure 3. Diversity reagents **15**{*1*−*12*}.

than three-quarters of the compounds analyzed were made in a purity greater than 75%. The average purity per reagent was then calculated for this truncated library and is shown in Tables 2−4. Except for the four reagents which were removed, most reagents performed well in the library.

Conclusion

The solid-phase synthesis of a 10 000 member 1,5-benzodiazepin-2-one library was achieved using the Irori directed sorting system. The Irori system was also used to remove the compounds of low yield from the library. The 1,5-benzodiazepin-2-one scaffold was prepared in solution and functionalized on resin. Despite the fairly stringent reaction conditions required, compounds were prepared in high yield and excellent purity. The screening of this library is in progress, and results from the screening will be reported elsewhere.

Experimental Section

General Information. Chloromethyl polystyrene beads of 150−300 μm (loading 2 mmol/g) were purchased from Polymer Laboratories. 4-hydroxy-2,6-dimethoxybenzaldehyde was purchased from Perseptive Biosystems. BAL resin was prepared according to the published procedure.[6a] A loading of 0.8 mmol/g was evaluated by loading 4-bromobenzylamine to the resin and using elemental analysis. Fmoc-Rink amide resin (loading 1.5 mmol/g, 150−300 μm beads) was purchased from Irori. All other reagents were purchased from standard commercial sources and used without further purification. Solvents used were EM Science of OmniSolv distilled grade unless specified otherwise. The following abbreviations were used: DCM = dichloromethane, DMF = dimethylformamide, THF = tetrahydrofuran. ^{1}H NMR and ^{13}C NMR spectra were recorded in 5 mm tubes on a 300 MHz Bruker ARX spectrometer in $CDCl_3$ unless otherwise stated. Mass spectra were recorded on Finnigan 4500 EI and Sciex API 3 IS spectrometers.

The library was constructed using the Irori Accutag system. MicroKans were filled with BAL resin or Fmoc-Rink resin by suspending the resin in an isobuoyant suspension (DMF:DCE−2:1) and dispensing the suspension with a Packard Multiprobe liquid handler. All reactions involving MicroKans were performed in round-bottom flasks equipped with overhead stirrers. The Autosort 10K was used to sort the MicroKans between combinatorial steps, and cleavage of the library compound was effected in the Accucleave 96. The validation set of 20 compounds was synthesized using Macrokans filled with 100 mg of resin, under the exact same conditions that were used for the library.

Preparation of 3-*N*-Phthalimido-1,5-benzodiazepine-2-one 9. 3-*N*-Boc-1,5-benzodiazepine-2-one[9b] (98 g, 355 mmol) was stirred in a 1:1 mixture or TFA:DCM (1.2 L) for 1 h. The mixture was evaporated, and the residue was azeotroped twice with toluene. The residue was dried under vacuum for 12 h. The residue was then suspended in toluene (1.2 L), and triethylamine (154 mL, 1 mol) was added followed by phthalic anhydride (52.9 g, 319 mmol). The flask was equipped with a Dean Stark apparatus and a condenser, and the mixture was heated at 110 °C overnight. The mixture was cooled to 0 °C and then filtered to afford **9** (73 g, 64%) as a bright yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.85 (m, 2H), 7.71 (m, 2H), 6.96 (m, 2H), 6.78 (m, 2H), 5.14 (dd, J = 4, 10 Hz, 1H), 4.16 (m, dd, J = 10, 13 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169, 167, 137, 134, 131, 124, 123, 121, 120, 119, 54, 45; MS (ESI) m/z = 307 $[M + H]^+$. Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.45; H, 4.23; N, 13.68. Found: C, 66.84; H, 4.30; N, 13.5.

Preparation of Resin Bound Amine 12{*1*−*19*}. For each amine, 585 MicroKans (each MicroKan contained 12 mg of 0.8 mmol/g loaded BAL resin) were placed into a 3.0 L three-necked round-bottom flask fitted with an overhead stirrer. The resin in the MicroKans was swelled in a 1% acetic acid in DMF solution (800 mL). The amine (45.0 mmol) and sodium triacetoxyborohydride (10.5 g, 45.0 mmol) were added sequentially. The reaction was stirred at room temperature for 5 h. For workup, each reaction was individually drained and washed with DMF (1×). All of the MicroKans were then combined and washed with 10% Et_3N in DMF (1×), DMF (3×), DCM (3×), and Et_2O(1×). The MicroKans were then dried overnight with a stream of nitrogen gas.

Preparation of Resin Bound Amine 12 (R1 = H). A total of 585 MicroKans (each MicroKan contained 9 mg of 1.5 mmol/g loaded Fmoc-Rink amide resin) were stirred for 2 h in 800 mL of a 1:1 mixture of DMF and piperidine. The MicroKans were then washed with DMF (4×), DCM (3×), and Et_2O (1×). The MicroKans were then dried overnight with a stream of nitrogen gas.

Preparation of Resin Bound Bromide 13. The MicroKans were reacted in two batches of 5265 MicroKans. For each batch, the MicroKans were suspended in anhydrous DCM (5 L), and bromoacetic acid (73.18 g, 520 mmol) was added followed by DIC (82.5 g, 520 mmol). The mixture was stirred overnight at room temperature and drained, and the MicroKans were washed with DCM (1×), DMF (3×), DCM (3×), and Et_2O (1×). The MicroKans were then dried overnight with a stream of nitrogen gas and then for 48 h in a vacuum oven.

Preparation of Resin Bound 1,5-Benzodiazepine-2-one Derivative 14. The MicroKans were reacted in two batches

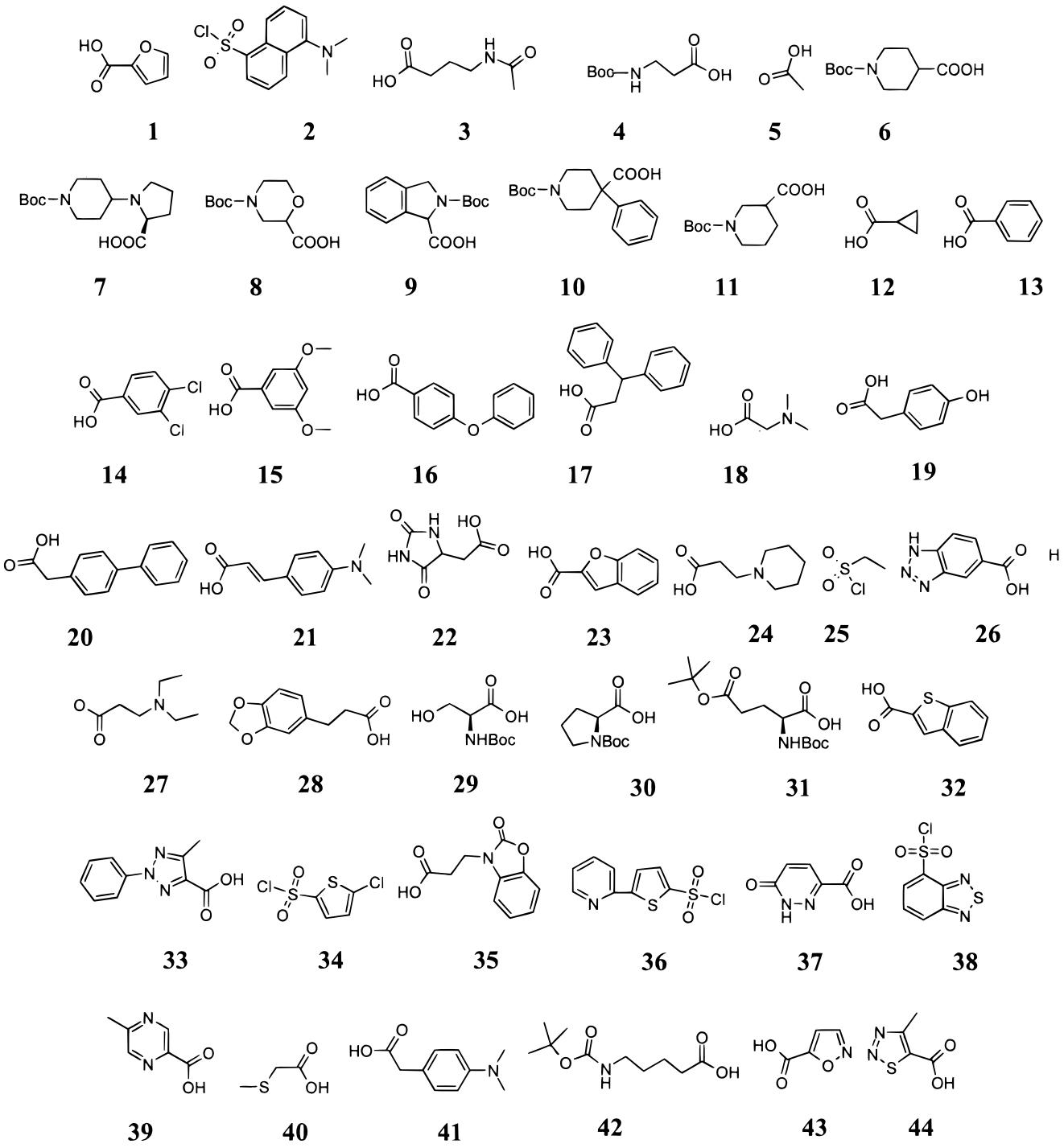


Figure 4. Diversity reagents **18** {*1*−*44*}.

of 5265 MicroKans in oven dried glassware. For each batch, the benzodiazepine scaffold (33.8 g, 110 mmol) was dissolved in anhydrous DMF, and potassium *tert*-butoxide (105 mL of a 1.0 M solution in THF) was added. The mixture was stirred for 30 min at room temperature, and the MicroKans were added in one portion. The mixture was stirred overnight at room temperature and drained, and the MicroKans were washed with DMF (3×), DCM (3×), and Et_2O (1×). The MicroKans were then dried overnight with a stream of nitrogen gas.

Preparation of 5-Alkyl-1,5-benzodiazepine-2-one Derivative 16. For each alkyl halide, 810 MicroKans were suspended in anhydrous DMF (1.2 L), and the halide (792 mmol) was added along with DIPEA (60 mL, 396 mmol) and potassium iodide (115 g, 396 mmol). The mixture was stirred overnight at 80 °C. For workup, each reaction was individually drained and washed with DMF (3×) and H_2O (1×). All of the MicroKans were then combined and washed with THF (1×), H_2O (1×), THF (2×), DCM (3×), and 2-propanol (1×).

Preparation of 5-Acyl- and 5-Sulfonyl-1,5-benzodiazepine-2-one Derivative 16. For each acid chloride or sulfonyl chloride, 810 MicroKans were suspended in anhydrous pyridine (1.2 L), and the acid chloride or sulfonyl

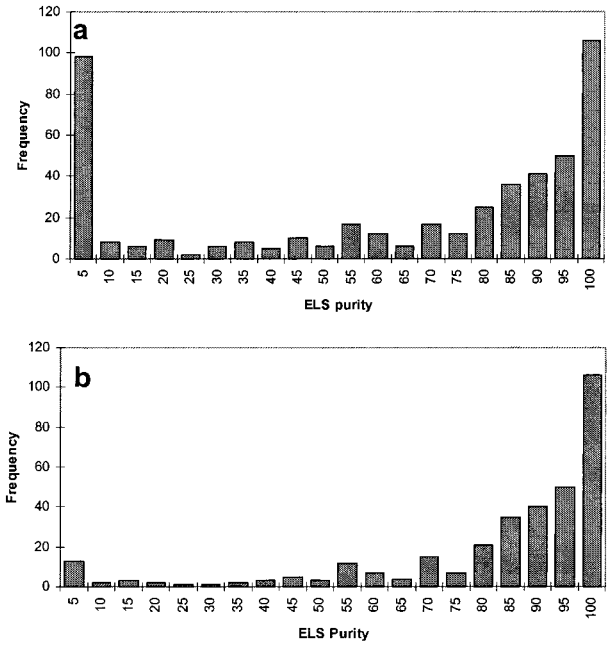


Figure 5. Purity distribution of a random selection of 5% of the library: (a) initial analysis and (b) after removal of the compounds containing **15**{*9*−*12*} at R2.

Table 2. Average Purity of Compounds Analyzed per R1

R1	ELS[a]	UV[b]	R1	ELS[a]	UV[b]
11{*1*}	89	73	**11**{*10*}	83	67
11{*2*}	87	68	**11**{*11*}	83	66
11{*3*}	90	71	**11**{*12*}	83	67
11{*4*}	90	70	**11**{*13*}	82	66
11{*5*}	70	55	**11**{*14*}	81	68
11{*6*}	69	54	**11**{*15*}	81	64
11{*7*}	83	62	**11**{*16*}	81	67
11{*8*}	85	67	**11**{*17*}	64	51
11{*9*}	78	59	no substituent[c]	56	47

[a] Average purity based on ELS detection. [b] Average purity based on UV detection. [c] Rink amide resin was used to release primary amides from the resin.

Table 3. Average Purity of Compounds Analyzed per R2

R2	ELS[a]	UV[b]	R2	ELS[a]	UV[b]
15{*1*}	92	76	**15**{*8*}	74	62
15{*2*}	83	64	**15**{*9*}	0	0
15{*3*}	75	59	**15**{*10*}	0	0
15{*4*}	86	72	**15**{*11*}	0	0
15{*5*}	65	52	**15**{*12*}	0	0
15{*6*}	83	64	no substituent	72	52
15{*7*}	84	70			

[a] Average purity based on ELS detection. [b] Average purity based on UV detection.

chloride (404 mmol) was added followed by a spoonful of DMAP. The mixture was stirred overnight at 80 °C. For workup, each reaction was individually drained and washed with DMF (2×). All of the MicroKans were then combined and washed with DMF (2×), 20% aqueous THF (3×), THF (2×), DCM (3×), and 2-propanol (1×).

Preparation of 5-(*N*-Alkyl-)-acyl-1,5-benzodiazepine-2-one Derivative 16. A total of 810 MicroKans were suspended in anhydrous toluene (1.2 L), and the isocyanate (404 mmol) was added. The mixture was stirred overnight at 40 °C. For workup, each reaction was individually drained and washed with DMF (2×). All of the MicroKans were then combined and washed with DMF (2×), 20% aqueous THF (3×), THF (2×), DCM (3×), and 2-propanol (1×).

Table 4. Average Purity of Compounds Analyzed per R3

R3	ELS[a]	UV[b]	R3	ELS[a]	UV[b]
18{*1*}	92	72	**18**{*24*}	57	47
18{*2*}	80	61	**18**{*25*}	48	32
18{*3*}	95	77	**18**{*26*}	74	54
18{*4*}	69	58	**18**{*27*}	78	54
18{*5*}	87	74	**18**{*28*}	79	63
18{*6*}	83	63	**18**{*29*}	86	67
18{*7*}	75	60	**18**{*30*}	88	76
18{*8*}	62	50	**18**{*31*}	71	65
18{*9*}	86	68	**18**{*32*}	97	78
18{*10*}	85	69	**18**{*33*}	94	77
18{*11*}	83	66	**18**{*34*}	73	50
18{*12*}	90	72	**18**{*35*}	94	74
18{*13*}	79	68	**18**{*36*}	66	51
18{*14*}	87	59	**18**{*37*}	87	70
18{*15*}	80	59	**18**{*38*}	72	53
18{*16*}	86	73	**18**{*39*}	81	65
18{*17*}	87	68	**18**{*40*}	75	63
18{*18*}	57	53	**18**{*41*}	91	76
18{*19*}	65	46	**18**{*42*}	74	59
18{*20*}	82	66	**18**{*43*}	74	58
18{*21*}	84	79	**18**{*44*}	84	73
18{*22*}	87	65	no substituent	88	69
18{*23*}	94	74			

[a] Average purity based on ELS detection. [b] Average purity based on UV detection.

Preparation of 3-Amino-1,5-benzodiazepine-2-one Derivative 17. The MicroKans were reacted in two batches of 5265 MicroKans. For each batch, the MicroKans were suspended in 25% hydrazine monohydrate in 2-propanol (5 L) and stirred at 50 °C for 4 h. The mixture was drained, and the MicroKans were washed with 2-propanol (3×), DMF (2×), and DCM (3×). The MicroKans were stirred overnight in DCM, drained, and washed with Et_2O (1×). The MicroKans were then dried overnight with a stream of nitrogen gas.

Preparation of 3-Acyl-1,5-benzodiazepine-2-one Derivative 19. For each carboxylic acid, 234 MicroKans were suspended in NMP (300 mL), and the carboxylic acid (28 mmol) was added followed by EDC (5.38 g, 28 mmol) or HBTU (10.6 g, 28 mmol) and DIEA (9.76 mL, 56 mmol). For the amine salts, additional DIEA (4.8 mL, 28 mmol) was added. The mixture was stirred overnight at room temperature. For workup, each reaction was individually drained and washed with DMF (1×). All of the MicroKans were then combined and washed with DMF (3×), THF (2×), DCM (3×), and ether (1×). The MicroKans were then dried overnight with a stream of nitrogen gas.

Preparation of 3-Sulfonyl-1,5-benzodiazepine-2-one Derivative 19. For each sulfonyl chloride, 234 MicroKans were suspended in DCM (300 mL), and the sulfonyl chloride (28 mmol) was added followed by Et_3N (3.91 mL, 28 mmol). The mixture was stirred overnight at room temperature. For workup, each reaction was individually drained and washed with DMF (1×). All of the MicroKans were then combined and washed with DMF (3×), THF (2×), DCM (3×), and ether (1×). The MicroKans were then dried overnight with a stream of nitrogen gas.

Cleavage of Compounds Attached to Rink Amide Resin. The MicroKans were sorted into cleavage racks. A solution of 10% TFA in DCM (1.5 mL) was added to each MicroKan. The mixture was shaken for 1 h and drained, the MicroKan was rinsed with DCM (1 mL), and the resulting solution was concentrated under reduced pressure to afford **20**.

Cleavage of Compounds Containing a *tert*-Butyl Ester. The MicroKans were sorted into cleavage racks. A solution of TFA (1.5 mL) was added to each MicroKan. The mixture was shaken for 1 h and drained, the MicroKan was rinsed with DCM (1 mL), and the resulting solution was concentrated under reduced pressure to afford **20**.

Cleavage of All Other Compounds. The MicroKans were sorted into cleavage racks. A solution of 50% TFA in DCM (1.5 mL) was added to each MicroKan. The mixture was shaken for 1 h and drained, the MicroKan was rinsed with DCM (1 mL), and the resulting solution was concentrated under reduced pressure to afford **20**.

2-(5-Acetyl-3-acetylamino-2-oxo-2,3,4,5-tetrahydro-benzo-[*b*][1,5]diazepin-1-yl)-*N*-(3-isopropoxy-propyl)-acetamide 20{*3,1,5*}: Yield 64%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−7.60 (m, 4H), 4.80 (m, 2H), 4.50 (t, J = 13 Hz, 1H), 4.32 (dd, J = 11, 15 Hz, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 3.52 (t, J = 5.8 Hz, 2H), 3.30 (m, 2H), 2.07 (s, 3H), 1.90 (s, 3H), 1.75 (m, 2H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172, 169.7, 167.9, 138.5, 134.3, 130.7, 129.5, 128.7, 124.6, 72.2, 66.7, 52.4, 51.8, 49.1, 38.7, 28.8, 22.4, 22.0, 21.9; MS (ESI) m/z = 419 [M + H]$^+$; HPLC (ELSD) 96%; HPLC (UV) 74%.

Furan-2-carboxylic Acid [2-Oxo-1-{[(Tetrahydro-furan-2-ylmethyl)-carbamoyl]-methyl}-5-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl]-amide 20{*1,2,1*}: Yield 49%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.60 (m, 10H), 7.10 (m, 1H), 6.50 (m, 1H), 4.80 (m, 1H), 4.40 (t, J = 12 Hz, 1H), 4.32 (dd, J = 3, 16 Hz, 1H), 4.15 (m, 1H), 4.05 (m, 1H), 3.8 (m, 2H), 3.50 (m, 2H), 3.35 (m, 1H), 2.44 (s, 3H), 1.9 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 168.8, 158.2, 146.3, 145.6, 144.4, 140.1, 140.0, 136.8, 131.2, 131.1, 130.7, 130.0, 127.0, 128.4, 123.9, 68.2, 55.1, 54.4, 52.49, 49.2, 43.5, 43.4, 28.6, 25.6, 21.5; MS (ESI) m/z = 568 [M + H]$^+$; HPLC (ELSD) 99%; HPLC (UV) 84%.

2-[5-Acetyl-3-(5-(dimethylamino)-naphthalene-1-sulfonylamino)-2-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]diazepin-1-yl]-*N*-(3,4-dimethoxy-benzyl)-acetamide 20{*2,1,2*}: Yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (t, J = 8 Hz, 2H), 8.03 (d, J = 9 Hz, 1H), 7.15−7.65 (m, 10H), 6.75 (m, 3H), 4.60 (t, J = 13 Hz, 1H), 4.00−4.3 (m, 4H), 3.8 (s, 3H0, 3.7 (s, 3H), 3.0 (s, 6H), 1.86 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.6, 169.5, 167.3, 149.1, 148.3, 138.5, 134.6, 130.8, 130.6, 129.9, 129.8, 129.1, 128.9, 128.4, 128.2, 124.6, 124.0, 120.1, 116.9, 111.3, 56.0, 55.9, 54.5, 52.7, 46.0, 43.2, 22.2,; MS (ESI) m/z = 661 [M + H]$^+$; HPLC (ELSD) 93%; HPLC (UV) 66%.

***N*-(5-Acetyl-1-cyclohexylcarbamoylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl)-3-amino-propionamide 20{*4,1,4*}:** Yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−7.60 (m, 4H), 4.80 (m, 2H), 4.50 (m), 3.55 (m, 2H), 3.20 (m, 2H), 2.65 (m, 2H), 1.80 (s, 3H), 1.60 (m, 4H), 1.10 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.8, 171.1, 170.7, 166.9, 138.7, 134.6, 130.5, 129.5, 128.4, 124.5, 54.4, 54.0, 32.4, 25.3, 24.8, 22.4; MS (ESI) m/z = 431 [M + H]$^+$; HPLC (ELSD) 93%; HPLC (UV) 76%.

***N*-{5-Acetyl-1-[(3,4-dimethoxy-benzylcarbamoyl)-methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl}-3-amino-propionamide 20{*2,1,4*}:** Yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−7.60 (m, 4H), 6.70 (m, 3H), 4.80 (m, 2H), 4.50 (m), 4.25 (m, 1H), 4.12 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.55 (m, 1H), 3.20 (m, 2H), 2.65 (m, 2H), 1.80 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.8, 171.1, 170.6, 168.0, 148.8, 148.1, 138.7, 134.6, 130.6, 129.5, 129.3, 119.8, 111.1, 55.8, 55.7, 54.4, 51.5, 43.3, 36.2, 32.1, 22.3; MS (ESI) m/z = 499 [M + H]$^+$; HPLC (ELSD) 91%; HPLC (UV) 55%.

Furan-2-carboxylic Acid (5-Acetyl-1-cyclohexylcarbamoylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]-diazepin-3-yl)-amide 20{*4,1,1*}: Yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.65 (m, 5H), 7.10 (m, 1H), 6.50 (m, 1H), 4.92 (m, 1H), 4.85 (m, 1H), 4.60 (dd, J = 9, 16 Hz, 1H), 4.40 (dd, J = 10, 16 Hz, 1H), 3.87 (m, 1H), 3.72 (m, 1H), 1.86 (s, 3H), 1.85−1.60 (m, 4H), 1.30−1.10 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.2, 170.1, 167.5, 158.52, 146.3, 145.2, 138.4, 138.3, 134.3, 130.8, 129.5, 128.8, 124.6, 54.4, 52.8, 52.1, 49.3, 48.8, 32.5, 25.3, 24.6, 22.0; MS (ESI) m/z = 454 [M + H]$^+$; HPLC (ELSD) 97%; HPLC (UV) 70%.

4-Acetylamino-*N*-{5-acetyl-1-[(3,4-dimethoxy-benzyl-carbamoyl)-methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo-[*b*][1,5]diazepin-3-yl}-butyramide 20{*2,1,3*}: Yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.15 (m, 4H), 6.80 (s, 3H), 4.70 (m, 2H), 4.60 (m, 1H), 4.40 (m, 1H), 4.30 (m, 1H), 3.80 (s, 6H), 3. 70 (m, 1H), 3.22 (m, 2H), 2.27 (m, 2H), 2.08 (s, 3H), 1.87 (s, 3H), 1.70 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.5, 171.9, 171.2, 167.8, 149.1, 148.4, 134.8, 130.7, 130.5, 129.7, 126.7, 124.5, 120.2, 111.4, 111.3, 56.0, 52.5, 51.8, 49.4, 43.6, 39.1, 33.3, 25.2, 22.9, 22.5; MS (ESI) m/z = 555 [M + H]$^+$; HPLC (ELSD) 93%; HPLC (UV) 60%.

Furan-2-carboxylic Acid (5-(3-Methylsulfanyl-propionyl)-2-oxo-1-{[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-methyl}-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl)-amide 20{*1,4,1*}: Yield 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.15 (m, 5H), 7.10 (m, 1H), 6.50 (m, 1H), 4.95 (m, 1H), 4.80 (m, 1H), 4.60 (m, 1H), 4.32 (m, 1H), 4.06 (m, 1H), 3.85 (m, 3H), 3.60 (m, 1H), 3.20 (m, 1H), 2.72 (t, J = 6 Hz, 1H), 2.47 (m, 1H), 2.30 (m, 1H), 2.00 (s, 3H), 1.90 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.1, 169.8, 168.1, 158.3, 146.4, 145.1, 138.8, 134.0, 130.7, 129.7, 128.6, 124.7, 115.8, 112.3, 68.2, 54.4, 52.5, 52.3, 48.7, 43.5, 34.0, 29.6, 28.6, 25.6, 15.7; MS (ESI) m/z = 516 [M + H]$^+$; HPLC (ELSD) 82%; HPLC (UV) 60%.

4-Acetylamino-*N*-(5-acetyl-1-cyclohexylcarbamoylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl)-butyramide 20{*4,1,3*}: Yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.15 (m, 4H), 4.70 (m, 2H), 4.40 (m, 2H), 3.70 (m, 2H), 3.30 (m, 2H), 2.35 (t, J = 7 Hz, 2H), 2.10 (s, 3H), 1.87 (s, 3H), 1.80 (m, 3H), 1.65 (m, 3H), 1.25 (m, 6H);

^{13}C NMR (300 MHz, $CDCl_3$) δ 174.4, 173.8, 172.5, 167.4, 138.4, 134.1, 130.9, 129.5, 128.8, 124.4, 54.4, 52.2, 51.6, 49.3, 39.5, 33.0, 32.5, 25.2, 24.6, 22.1, 21.8; MS (ESI) m/z = 487 $[M + H]^+$; HPLC (ELSD) 92%; HPLC (UV) 60%.

4-Acetylamino-*N*-{5-acetyl-1-[(3-isopropoxy-propylcarbamoyl)-methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-[1,5]diazepin-3-yl}-butyramide 20{*3,1,3*}: Yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.15 (m, 4H), 4.75 (m, 2H), 4.40 (m, 2H), 3.75 (m, 1H), 3.63 (t, J = 6 Hz, 1H), 3.55(t, J = 6 Hz, 2H), 3.30 (m, 4H), 2.35 (t, J = 7 Hz, 2H), 2.10 (s, 3H), 1.90 (s, 3H), 1.80 (m, 4H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.5, 174.0, 172.9, 169.8, 168.3, 138.3, 134.0, 131.0, 129.5, 128.9, 124.5, 72.5, 66.4, 52.1, 51.6, 49.2, 39.5, 38.5, 33.0, 28.7, 24.6, 22.0, 21.8; MS (ESI) m/z = 505 $[M + H]^+$; HPLC (ELSD) 95%; HPLC (UV) 74%.

2-(5-Acetyl-3-acetylamino-2-oxo-2,3,4,5-tetrahydro-benzo-[*b*][1,5]diazepin-1-yl)-*N*-cyclohexyl-acetamide 20{*4,1,5*}: Yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.15 (m, 4H), 4.73 (m, 2H), 4.57 (t, J = 6 Hz, 1H), 4.32 (t, J = 6 Hz, 1H), 3.75 (m, 2H), 2.10 (s, 3H), 1.90 (s, 3H), 1.85 (m, 1H), 1.65 (m, 3H), 1.25 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.2, 170.0, 169.9, 167.3, 167.2, 138.5, 134.3, 130.8, 129.4, 127.2, 124.6, 54.4, 52.7, 52.6, 51.8, 49.2, 32.6, 32.4, 25.2, 24.6, 22.4, 22.1; MS (ESI) m/z = 401 $[M + H]^+$; HPLC (ELSD) 92%; HPLC (UV) 64%.

Furan-2-carboxylic Acid {5-Acetyl-1-[(3-isopropoxy-propylcarbamoyl)-methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl}-amide 20{*3,1,1*}: Yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.10 (m, 5H), 7.10 (m, 1H), 6.55 (m, 1H), 4.95 (m, 1H), 4.80 (m, 1H), 4.55 (m, 1H), 4.35 (m, 1H), 3.85 (m, 1H), 3.60 (m, 1H), 3.55 (m, 2H), 3.38 (m, 2H), 1.90 (s, 3H), 1.75 (m, 2H), 1.14 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.4, 169.8, 168.2, 158.5, 146.2, 145.2, 138.4, 134.3, 130.8, 129.5, 128.8, 124.6, 116.1, 112.4, 72.3, 66.5, 54.4, 52.4, 52.1, 48.7, 38.7, 28.7, 21.9; MS (ESI) m/z = 472 $[M + H]^+$; HPLC (ELSD) 91%; HPLC (UV) 63%.

Furan-2-carboxylic Acid [2-Oxo-1-{[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-methyl}-5-(4-trifluoromethyl-benzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl]-amide 20{*1,3,1*}: Yield 39%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.15 (m, 9H), 7.10 (m, 1H), 6.55 (m, 1H), 4.95 (m, 1H), 4.80 (m, 1H), 4.55 (m, 1H), 4.18 (d, J = 4 Hz, 1H), 3.85 (m, 1H), 3.70−3.10 (m, 5H), 1.85 (m, 3H), 1.40 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.9, 169.7, 169.5, 158.4, 146.1, 145.2, 143.0, 142.1, 140.7, 135.0, 128.8, 128.4, 125.8, 125.7, 125.5, 123.7, 121.2, 116.0, 112.4, 68.1, 68.0, 61.2, 56.9, 52.2, 51.9, 49.2, 49.1, 43.6, 42.9, 28.6, 28.0, 25.6, 25.5; MS (ESI) m/z = 572 $[M + H]^+$; HPLC (ELSD) 96%; HPLC (UV) 68%.

2-[5-Acetyl-3-(5-(dimethylamino)-naphthalene-1-sulfonylamino)-2-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]diazepin-1-yl]-*N*-(3-isopropoxy-propyl)-acetamide 20{*3,1,2*}: Yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 8 Hz, 1H), 8.58 (d, J = 8 Hz, 1H), 8.10 (d, J = 9 Hz, 1H), 7.15−7.65 (m, 7H), 4.80−4.60 (m), 4.10 (m, 1H), 3.50−3.40 (m, 5H), 3.25 (s, 6H), 3.20 (m, 2H), 1.80 (s, 3H), 1.60 (m, 2H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.8, 169.4, 167.4, 138.9, 136.3, 134.8, 130.8, 130.2, 130.0, 129.6, 128.6, 128.3, 127.9, 125.3, 124.5, 124.3, 117.7, 116.7, 112.9, 72.1, 66.3, 54.7, 52.9, 51.6, 46.5, 37.9, 37.8, 29.5, 22.5, 22.2.; MS (ESI) m/z = 611 $[M + H]^+$; HPLC (ELSD) 96%; HPLC (UV) 60%.

4-Acetylamino-*N*-(5-acetyl-2-oxo-1-{[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-methyl}-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl)-butyramide 20{*1,1,3*}: Yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.15 (m, 4H), 4.72 (m, 2H), 4.47 (m, 2H), 4.05 (m, 1H), 3.80 (m, 4H), 3.50 (m, 1H), 3.22 (m, 2H), 3.15 (m, 1H), 2.37 (m, 2H), 2.10−1.80 (m, 10H), 1.55 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.4, 173.9, 172.7, 169.9, 168.4, 138.4, 134.2, 130.8, 129.5, 128.8, 124.5, 68.2, 54.4, 52.0, 51.6, 49.2, 43.7, 39.5, 33.0, 28.2, 25.5, 24.5, 22.0, 21.8; MS (ESI) m/z = 489 $[M + H]^+$; HPLC (ELSD) 89%; HPLC (UV) 70%.

2-(5-Acetyl-3-acetylamino-2-oxo-2,3,4,5-tetrahydro-benzo-[*b*][1,5]diazepin-1-yl)-*N*-(3,4-dimethoxy-benzyl)-acetamide 20{*2,1,5*}: Yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.15 (m, 4H), 6.80 (s, 3H), 4.80−4.50 (m, 3H), 4.40−4.20 (m, 3H), 3.80 (s, 6H), 3. 70 (m, 1H), 2.08 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.5, 169.9, 168.2, 168.1, 149.0, 148.5, 138.4, 134.2, 130.9, 129.8, 129.7, 129.5, 128.9, 124.6, 120.1, 111.2, 55.8, 54.4, 52.4, 51.7, 49.2, 43.7, 22.3. 22.0; MS (ESI) m/z = 470 $[M + H]^+$; HPLC (ELSD) 94%; HPLC (UV) 70%.

Furan-2-carboxylic Acid (5-Acetyl-2-oxo-1-{[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-methyl}-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl)-amide 20{*1,1,1*}: Yield 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.15 (m, 9H), 7.10 (m, 1H), 6.55 (m, 1H), 4.95 (m, 1H), 4.80 (m, 1H), 4.55 (m, 2H), 4.05 (m, 1H), 3.70−3.50 (m, 3H), 3.55 (m, 1H), 3.20 (m, 1H), 2.10−1.80 (m, 6H), 1.40 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.4, 169.8, 168.3, 158.4, 146.3, 145.1, 138.4, 134.4, 130.8, 129.5, 128.8, 124.7, 115.9, 112.3, 68.2, 54.4, 52.4, 52.2, 48.6, 43.5, 28.6, 25.6, 22.0; MS (ESI) m/z = 455 $[M + H]^+$; HPLC (ELSD) 99%; HPLC (UV) 87%.

2-[5-Acetyl-3-(5-(dimethylamino)-naphthalene-1-sulfonylamino)-2-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]diazepin-1-yl]-*N*-cyclohexyl-acetamide 20{*4,1,2*}: Yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 8 Hz, 2H), 8.10 (d, J = 9 Hz, 1H), 7.15−7.65 (m, 7H), 4.70 (t, J = 13 Hz, 1H), 4.40 (m), 4.10 (m, 2H), 3.50 (m, 1H), 3.25 (s, 6H), 1.80 (s, 3H), 1.70 (m, 4H), 1.20 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.7, 169.6, 166.5, 136.1, 134.6, 130.7, 130.0, 129.9, 129.2, 129.0, 128.5, 128.3, 124.8, 124.2, 123.2, 117.2, 54.6, 52.9, 52.8, 51.8, 46.2, 32.8, 32.6, 25.6, 25.0, 22.4; MS (ESI) m/z = 593 $[M + H]^+$; HPLC (ELSD) 97%; HPLC (UV) 70%.

Furan-2-carboxylic Acid {5-Acetyl-1-[(3,4-dimethoxy-benzylcarbamoyl)-methyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,5]diazepin-3-yl}-amide 20{*2,1,1*}: Yield 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.25 (m, 5H), 7.06 (d, J = 4 Hz, 1H), 6.83−6.70 (m, 3H), 6.50 (m, 1H), 4.95 (m, 1H), 4.80 (t, J = 12 Hz, 1H), 4.62 (m, 1H), 4.45 (m, 1H), 4.30 (m, 2H), 3.81 (m, 7H), 1.87 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.1, 170.1, 167.8, 167.7, 149.0, 148.2, 146.9, 144.8, 139.1, 134.8, 130.6, 130.5, 129.6, 129.5, 128.4,

124.7, 116.4, 115.3, 112.2, 111.0, 55.9, 55.8, 52.8, 51.9, 43.4, 43.3, 22.2; MS (ESI) $m/z = 522$ $[M + H]^+$; HPLC (ELSD) 97%; HPLC (UV) 57%.

2-(5-Acetyl-3-acetylamino-2-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,5]diazepin-1-yl)-*N*-(tetrahydro-furan-2-ylmethyl)-acetamide 20{*1,1,5*}: Yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.15(m, 4H), 4.80 (m, 1H), 4.75 (m, 1H), 4.45 (m,2H), 4.05 (m, 1H), 3.80 (m, 3H), 3.50 (m, 1H), 3.15 (m, 1H), 2.07 (s, 3H), 1.95 (m, 3H), 1.89 (s, 3H), 1.60 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.5, 172.3, 169.8, 168.3, 138.4, 134.3, 130.8, 129.5, 128.8, 124.6, 68.2, 54.4, 52.3, 51.9, 49.1, 43.6, 28.6, 25.6, 22.3, 22.0; MS (ESI) $m/z = 403$ $[M + H]^+$; HPLC (ELSD) 93%; HPLC (UV) 75%.

Supporting Information Available. ^{1}H NMR, ^{13}H NMR, and MS spectra as well as HPLC traces for all 20 compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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