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New Four-Component Ugi-Type Reaction. Synthesis of Heterocyclic Structures Containing a Pyrrolo[1,2-*a*][1,4]diazepine Fragment

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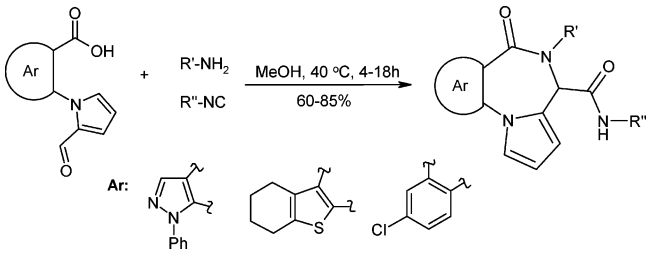

We present a convenient synthesis of novel heterocyclic structures containing pyrrolo[1,2-*a*][1,4]diazepine fragment using a novel modification of four-component Ugi condensation. We demonstrate the usefulness and versatility of the developed approach for the synthesis of variously substituted compounds and discuss the scope and limitations of the chemistry involved.

Among a variety of physiologically active diazepines, the derivatives of pyrrolo[1,2-*a*][1,4]benzodiazepines and their bioisosteric analogues represent a relatively little-explored group with interesting pharmaceutical properties. In particular, they were described as antitumor agents acting against various types of leukemia cell lines[1] and CNS active agents.[2] A series of structurally related imidazo[1,5-*a*][1,4]benzodiazepines entered preclinical and clinical trials as agonists or antagonists of benzodiazepine receptors;[3] one of them, Flumazenil,[4] was launched into market as neurologic drug. According to these examples, differently substituted pyrrolo[1,2-*a*][1,4]benzodiazepines and their modified analogues with bioisosterically transformed benzene and pyrrole rings represent promising synthetic targets. Development of efficient synthetic approaches to the related scaffolds will provide a valuable source of novel physiologically active agents.

Depending on the substitution pattern of pyrrolo[1,2-*a*][1,4]diazepines, several synthetic approaches are possible. For instance, synthetic approaches to pyrrolo[1,2-*a*]-[1,4]benzodiazepines based on Mannich reaction between 1-(2-aminomethylphenyl)-1*H*-pyrrole and aldehydes or ketones were developed.[2d,5] Syntheses of pyrrolothieno-[1,4]diazepines utilizing 3-(2-formyl-1*H*-pyrrol-1-yl)-2-thiophenecarboxamide[6] or 2-(2-formyl-1*H*-pyrrol-l-yl)-3-thiophenecarbonitrile[7] as starting materials were reported. The synthetic pathway leading to 5,6-dihydro-4*H*-furo-[3,2-*f*]pyrrolo[1,2-*a*][1,4]diazepines was described starting from α-bromophenones via 2-amino-3-furonitriles.[8] However, the described synthetic strategies still have limitations in terms of the possible substituents around the core scaffold.

In this work, we describe an efficient synthetic route to aryl- and heteroaryl-fused carboxamide derivatives of the pyrrolo[1,2-*a*][1,4]diazepine heterocycle, which were not previously reported in the literature. Our synthetic method is based on the four-component Ugi reaction between aldehyde, amine, isonitrile, and carboxylic acid, which has emerged as a powerful tool for rapid identification and optimization of lead compounds in drug discovery.[9] One important modification of this reaction is the use of bifunctional reagents. In particular, modified syntheses using bifunctional keto acids (or aldehyde acids), amine, and isonitrile as starting materials have been reported. For example, reaction of ω-ketoacids[10] or aldehydes[11] with the corresponding isonitriles and amines led to β-lactams. A series of 2,3-dihydro-1*H*-isoindole-3-ones was prepared from 2-formylbenzoic acid.[12] Using 1,8-naphthalaldehydic acid, 2-formylphenoxyacetic acid, and 2′-formylphenoxy-2-benzoic acid as the bifunctional reagents in Ugi coupling, a series of rare six-, seven-, and eight-membered heterocyclic rings was obtained.[12] Recently, Marcaccini et al. reported a synthetic approach to novel *S*,*N*-heterocycles, starting from the corresponding thiacarboxylic keto acids.[13] In this context, the synthetic approach to the title structures developed in this work can be referred to as an evolutionary modification

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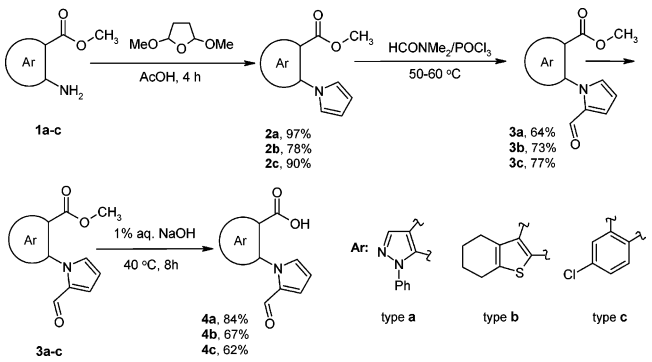
SCHEME 1. Synthesis of Bifunctional Reagents for Ugi Condensation



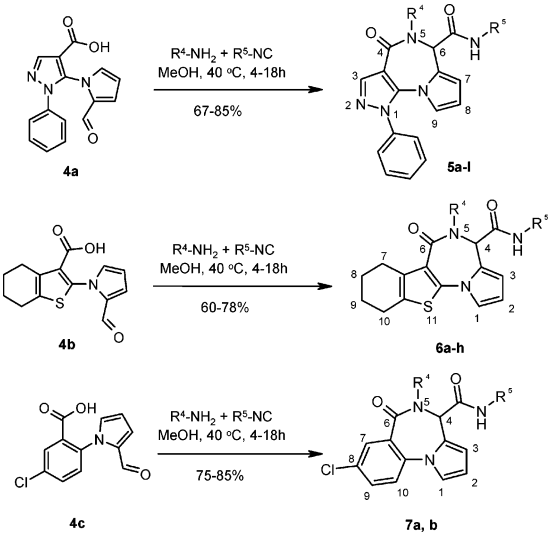
of the classical Ugi four-component reaction with the use of bifunctional reagents.

In the first part of our work, syntheses of novel bifunctional reagents for Ugi condensation **4a**−**c** were accomplished (Scheme 1). The commercially available aminocarboxylates **1a**−**c** were easily converted to the corresponding 1*H*-pyrrol-1-yl derivatives **2a**−**c** using reaction with 2,5-dimethoxytetrahydrofuran in acetic acid (yields 78−97%). Treatment of **2a**−**c** with $POCl_3$ at 50−60 °C in the presence of DMF led to 2-formyl-1*H*-pyrroles **3a**−**c** in good yields (64−77%). Esters **3a**−**c** were hydrolyzed by aqueous alkali to furnish the desired aldehyde acids **4a**−**c** in good yields (62−84%).

At the next step, we used a novel approach to the pyrrolo[1,2-*a*][1,4]diazepine heterocycles based on a novel modification of the Ugi four-component reaction. The Ugi condensation can be readily applied in combinatorial chemistry approaches and is an effective synthetic method to the assembly of differently substituted derivatives of benzodiazepine.[14] In this work we have found that the reaction of aldehyde acids **4a**−**c** with the corresponding isonitriles and amines in methanol at 40 °C led to novel pyrrolo[1,2-*a*][1,4]diazepine heterocyclic structures **5a**−**l** (yield 67−85%), **6a**−**h** (yield 60−78%), and **7a,b** (yield 75−85%) (Scheme 2), which were not previously described in scientific literature.

The reaction presumably follows the same initial course as the classical Ugi condensation with an intermediate imine being attacked by the isonitrile to give a nitrilium intermediate, which then undergoes intramolecular cyclization.[9] As a synthetic tool for creating diverse compound libraries, the developed Ugi-type condensation offers a large number of various amines and isonitriles. We have observed that the nature of the initial heterocyclic core moieties (e.g., types **a**−**c**) does not substantially affect the reaction yield and time, and various aldehyde acids **4a**−**c** could be used. With respect to amine component, various aliphatic and aromatic primary amines, such as substituted anilines, linear and branched aliphatic amines, and nitrogen-containing compounds, were tolerated without any limitations. A restriction is the limited number of commercially or synthetically

SCHEME 2. Four-Component Ugi Condensation



available isonitriles. In this work, we used carbocyclic isonitriles available from commercial sources. Structures and yields of the synthesized compounds are shown in Table 1.

In summary, we have shown that pyrrolo[1,2-*a*][1,4]-diazepine heterocycles can be efficiently prepared by a novel modification of four-component Ugi reaction of bifunctional aldehyde-acids, isonitriles, and amines. Considering the ease of the preparation of initial reactants, convenient synthesis, and isolation of products and the overall good chemical yields of the described transformations, this route provides a new valuable entry to novel heterocycle-fused analogues of biologically active pyrrolo-[1,2-*a*][1,4]diazepines and their bioisosteric analogues. As a synthetic tool for creating diverse compound libraries, the four-component condensation used in this work offers a large number of potential input reactants and resulting products. The obtained compounds represent valuable starting points for the development of compounds of biological interest. The use of compounds from series **5**−**7** in the search for novel bioactive agents is under investigation at Chemical Diversity, Inc. and will be reported in due course.

Experimental Section

General Procedure for Preparation of Aryl-Fused 3-Oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepine-1-carboxylic Acid Amides 5−**7**. Equimolar amounts of compounds **4a**−**c**, the isonitrile, and the corresponding amine were dissolved in methanol to an approximate concentration of 1 M in each component. The reaction mixture was stirred at 40 °C for 4−18 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). On completion, the reaction mixture was cooled to room temperature, and the formed precipitate was filtered out and purified (if desired) by recrystallization from diethyl ether or by chromatography on silica gel, eluting with a gradient of 0−10% MeOH in CH_2Cl_2.

***N*-Cyclohexyl-5-(3-methoxybenzyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide 5a:** mp 186−189 °C; IR (KBr, cm^{-1}) ν 1630 (CO), 1670 (CO), 3330 (NH); ^1H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.75−1.7 (m, 10 H), 3.26−3.3 (m, 1 H), 3.73 (s, 3 H), 4.67 (d, J = 2.3 Hz, 1 H), 4.8 (d, J = 2.3 Hz, 1 H), 5.35 (s, 1 H), 6.0−6.1 (d, J = 4.9 Hz, 2 H), 6.15−6.22 (s, 1 H), 6.8 (d, J = 4.0 Hz, 1 H), 7.0−7.1 (d+d, J = 7.3 Hz, 2 H), 7.2−7.29 (t, J = 7.3 Hz, 1 H), 7.38−7.51 (m, 5 H), 7.82 (s, 1 H); HRMS *m/z* 510.2493 (M^+).

5-(2-Chlorobenzyl)-*N*-cyclohexyl-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-

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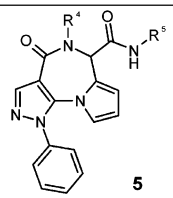
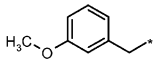
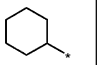
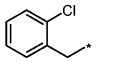
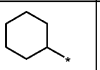
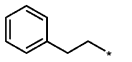
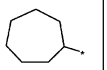
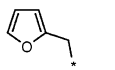
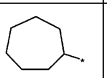
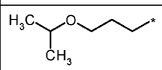
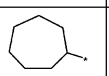
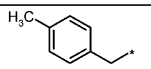
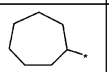
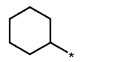
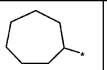
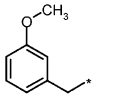
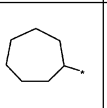
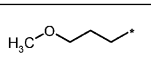
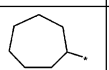
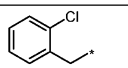
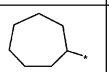
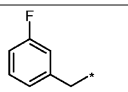
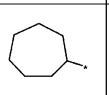
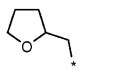
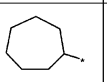
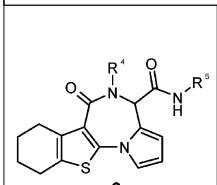
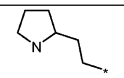
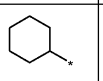
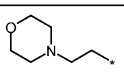
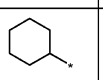
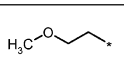
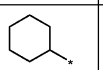
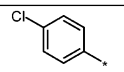
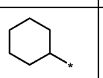
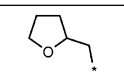
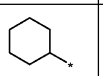
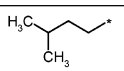
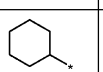
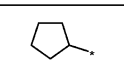
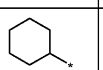
TABLE 1. Structures and Yields of Compounds 5a–l, 6a–h, and 7a,b[a]

Structure	Entry	R^4	R^5	Yield,%
 **5**	**a**			77
	b			68
	c			78
	d			69
	e			67
	f			85
	g			71
	h			83
	i			77
	j			74
	k			84
	l			69
 **6**	**a**			71
	b			66
	c			73
	d			78
	e			75
	f			61
	g			72
	h			60
7	**a**			75
	b			85

[a] All compounds were obtained as racemic mixtures of enantiomers. The assignment of these structures was made on the basis of ^{1}H NMR and high-resolution mass-spectroscopy. The ^{1}H NMR spectra of compounds **5**–**7** contain the single aliphatic proton of the diazepine ring, which can be seen as a characteristic singlet in the range of δ 5.11–5.48. The characteristic aromatic protons of the pyrrole ring can be seen as doublets at δ 6.2–6.9 Hz (H-2) and δ 5.8–6.3 Hz (H-4).

carboxamide 5b: mp 138–141 °C; IR (KBr, cm^{-1}) ν 1625 (CO), 1675 (CO), 3325 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.0–1.75 (m, 10 H), 3.3–3.48 (m, 1 H), 4.5–4.6 (d, J = 2.0 Hz, 1 H), 5.16 (s, 1 H), 5.3–5.44 (d, J = 2.0 Hz, 1 H), 5.75–5.8 (t, J = 8.4 Hz, 1 H), 6.0 (d, J = 7.9, 1 H), 6.22 (d, J = 7.9 Hz, 1 H), 7.0–7.5 (m, 10 H), 7.86 (s, 1 H); HRMS *m/z* 514.2005 (M^+).

***N*-Cycloheptyl-4-oxo-1-phenyl-5-(2-phenylethyl)-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide 5c:** mp 164–167 °C; IR (KBr, cm^{-1}) ν 1620 (CO), 1680 (CO), 3310 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.1–1.63 (m, 12 H), 2.7–2.84 (m, 1 H), 2.9–3.08 (m, 1 H), 3.5–3.69 (m, 2 H), 4.0–4.2 (m, 1 H), 5.5 (s, 1 H), 6.07–6.1 (t, J = 8.2 Hz, 1 H), 6.21 (d, J = 7.7 Hz, 1 H), 6.27 (d, J = 7.7 Hz, 1 H), 7.0–7.08 (d, J = 4.2 Hz, 1 H), 7.1–7.22 (m, 5 H), 7.37–7.5 (m, 5 H), 7.8 (s, 1 H); HRMS *m/z* 508.2703 (M^+).

***N*-Cycloheptyl-5-(2-furylmethyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide 5d:** mp 157–161 °C; IR (KBr, cm^{-1}) ν 1630 (CO), 1670 (CO), 3340 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.09–1.64 (m, 12 H), 3.46–3.6 (m, 1 H), 4.7 (d, J = 2.6 Hz, 1 H), 4.84 (d, J = 2.6 Hz, 1 H), 5.25 (s, 1 H), 6.0–6.1 (m, 2 H), 6.11–6.17 (t, J = 8.5 Hz, 1 H), 6.35–6.4 (d, J = 7.8 Hz, 1 H), 6.46 (d, J = 7.8 Hz, 1 H), 6.6 (d, J = 5.2 Hz, 1 H), 7.31–7.57 (m, 6 H), 7.81 (s, 1 H); HRMS *m/z* 484.2341 (M^+).

***N*-Cycloheptyl-5-(3-isopropoxypropyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-6-carboxamide 5e**: mp 143–145 °C; IR (KBr, cm^{-1}) ν 1630 (CO), 1660 (CO), 3330 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.1–1.2 (s, 6 H), 1.23–1.7 (m, 12 H), 1.66–1.7 (m, 1 H), 1.7–1.87 (m, 1 H), 3.3–3.55 (m, 4 H), 3.59–3.7 (m, 1 H),

3.85−4.1 (m, 1 H), 5.3 (s, 1 H), 6.05−6.1 (t, J = 8.2 Hz, 1 H), 6.2 (d, J = 7.7 Hz, 1 H), 6.28 (d, J = 7.7 Hz, 1 H), 7.05−7.12 (br s, 1 H), 7.35−7.57 (m, 5 H), 7.8 (s, 1 H); HRMS *m/z* 504.2963 (M^+).

***N*-Cycloheptyl-5-(4-methylbenzyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide 5f:** mp 210−212 °C; IR (KBr, cm^{-1}) ν 1635 (CO), 1680 (CO), 3380 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.8−1.55 (m, 12 H), 2.21 (s, 3 H), 3.35−3.46 (m, 1 H), 4.54 (d, J = 2.7 Hz, 1 H), 4.9 (d, J = 2.7 Hz, 1 H), 5.3 (s, 1 H), 6.05 (t, J = 8.2 Hz, 1 H), 6.1 (d, J = 7.7 Hz, 1 H), 6.18 (d, J = 7.7 Hz, 1 H), 7.15 (d, J = 7.3 Hz, 2 H), 7.3−7.5 (m, 7 H), 7.82 (s, 1 H), HRMS *m/z* 508.2702 (M^+).

***N*-Cycloheptyl-5-cyclohexyl-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide 5g:** mp 227−234 °C; IR (KBr, cm^{-1}) ν 1630 (CO), 1655 (CO), 3400 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.09−2.1 (m, 22 H), 3.5−3.67 (m, 1 H), 4.41−4.6 (m, 1 H), 5.4 (s, 1 H), 6.07 (t, J = 8.6 Hz, 1 H), 6.15 (d, J = 7.9 Hz, 1 H), 6.24 (d, J = 7.9 Hz, 1 H), 6.6−6.8 (d, J = 4.4 Hz, 1 H), 7.3−7.5 (m, 5 H), 7.8 (s, 1 Hz H); HRMS *m/z* 482.2474 (M^+).

***N*-Cycloheptyl-5-(3-methoxybenzyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-6-carboxamide 5h:** mp 179−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.8−1.53 (m, 12 H), 3.38−3.5 (m, 1 H), 3.75 (s, 3 H), 4.51 (d, J = 2.8 Hz, 1 H), 4.88 (d, J = 2.8 Hz, 1 H), 5.32 (s, 1 H), 6.0 (s, 1 H), 6.01 (t, J = 8.4 Hz, 1 H), 6.07 (d, J = 7.8 Hz, 1 H), 6.14 (d, J = 7.8 Hz, 1 H), 6.8 (d, J = 5.2 Hz, 1 H), 7.0−7.1 (m, 2 H), 7.19−7.3 (m, 1 H), 7.36−7.5 (m, 5 H), 7.84 (s, 1 H); HRMS *m/z* 524.2651 (M^+).

***N*-Cycloheptyl-5-(3-methoxypropyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-6-carboxamide 5i:** mp 150−152 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.1−1.64 (m, 12 H), 1.66−2.0 (2m, 2 H), 3.25 (s, 3 H), 3.3−3.38 (m, 2 H), 3.5−3.65 (m, 2 H), 3.72−3.9 (m, 1 H), 5.27 (s, 1 H), 6.05 (t, J = 8.3 Hz, 1 H), 6.16 (d, J = 7.7 Hz, 1 H), 6.2 (d, J = 7.7 Hz, 1 H), 7.2 (d, J = 3.8 Hz, 1 H), 7.35−7.5 (m, 5 H), 7.79 (s, 1 H); HRMS *m/z* 476.2652 (M^+).

5-(2-Chlorobenzyl)-*N*-cycloheptyl-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide 5j: mp 121−123 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.2−1.6 (m, 12 H), 3.55−3.67 (m, 1 H), 4.5−4.59 (d, J = 2.0 Hz, 1 H), 5.15 (s, 1 H), 5.26−5.4 (d, J = 2.0 Hz, 1 H), 5.75−5.84 (t, J = 8.4 Hz, 1 H), 5.94−6.07 (d, J = 7.8 Hz, 1 H), 6.13−6.24 (d, J = 7.8 Hz, 1 H), 6.95−7.0 (m, 1 H), 7.15−7.8 (m, 4 H), 7.82−7.51 (m, 5 H), 7.8 (s, 1 H); HRMS *m/z* 528.2154 (M^+).

***N*-Cycloheptyl-5-(3-fluorobenzyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine-6-carboxamide 5k:** mp 123−126 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.0−1.63 (m, 12 H), 3.50−3.62 (m, 1 H), 4.68−4.76 (d, J = 2.2 Hz, 1 H), 4.82−4.9 (d, J = 2.2 Hz, 1 H), 5.4 (s, 1 H), 6.0−6.15 (m, 2 H), 6.17 (d, J = 8.2 Hz, 1 H), 6.27−6.45 (m, 1 H), 6.97−7.05 (t(F), J = 9.0 Hz, 1 H), 7.2−7.4 (t(F), J = 9.1 Hz, 2 H), 7.41−7.5 (m, 6 H), 7.8 (s, 1 H); HRMS *m/z* 512.2452 (M^+).

***N*-Cycloheptyl-4-oxo-1-phenyl-5-(tetrahydrofuran-2-ylmethyl)-1,4,5,6-tetrahydropyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-6-carboxamide 5l:** mp 162−165 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.0−2.17 (m, 16 H), 3.0−3.12 (m, 1 H), 3.55−4.17 (m, 4 H), 4.3−4.4 (m, 1 H), 4.5−4.6 (t, J = 2.6 Hz, 1 H), 5.3 (s, 1 H), 5.5 (s, 1 H), 6.05 (t, J = 8.5 Hz, 1 H), 6.15 (d, J = 7.9 Hz, 1 H), 6.16 (d, J = 7.9 Hz, 1 H), 7.3−7.5 (m, 5 H), 7.78 (s, 1 H), 7.9 (d, J = 6.3 Hz, 1 H); HRMS *m/z* 488.265 (M^+).

***N*-Cyclohexyl-6-oxo-5-(2-pyrrolidin-2-ylethyl)-5,6,7,8,9,-10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-4-carboxamide 6a:** mp 189−192 °C; IR (KBr, cm^{-1}) ν 1635 (CO), 1675 (CO), 3200 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.75−3.45 (m, 30 H), 4.37−4.52 (t, J = 3.1 Hz, 1 H), 5.15 (s, 1 H), 6.17 (s, 2 H), 6.8 (s, 1 H), 8.15−8.3 (br s, 1 H); HRMS *m/z* 481.2633 (M^+).

***N*-Cyclohexyl-5-(2-morpholin-4-ylethyl)-6-oxo-5,6,7,8,9,-10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-4-carboxamide 6b:** mp 180−182 °C; IR (KBr, cm^{-1}) ν 1640 (CO), 1675 (CO), 3250 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.85−3.77 (m, 30 H), 4.2−4.4 (t, J = 3.4 Hz, 1 H), 5.2 (s, 1 H), 6.19 (s, 2 H), 6.8 (s, 1 H), 7.1−7.2 (br s, 1 H); HRMS *m/z* 497.2576 (M^+).

***N*-Cyclohexyl-5-(2-methoxyethyl)-6-oxo-5,6,7,8,9,10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-4-carboxamide 6c:** mp 157−159 °C; IR (KBr, cm^{-1}) ν 1630 (CO), 1670 (CO), 3300 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.76−3.73 (m, 22 H), 3.33 (s, 3 H), 4.13 (s, 1 H), 5.17 (s, 1 H), 6.18 (s, 2 H), 6.84 (s, 1 H), 6.5−6.69 (br s, 1 H); HRMS *m/z* 442.2152 (M^+).

5-(4-Chlorophenyl)-*N*-cyclohexyl-6-oxo-5,6,7,8,9,10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-4-carboxamide 6d: mp 216−218 °C; IR (KBr, cm^{-1}) ν 1630 (CO), 1685 (CO), 3400 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.8−3.0 (m, 18 H), 3.31−3.49 (s, 1 H), 5.35 (s, 1 H), 6.8−6.0 (br s, 1 H), 6.23 (s, 2 H), 6.91 (s, 1 H), 7.2−7.4 (m, 4 H); HRMS *m/z* 494.1661 (M^+).

***N*-Cyclohexyl-6-oxo-5-(tetrahydrofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo-[1,2-*a*][1,4]diazepine-4-carboxamide 6e:** mp 168−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 1.0−3.2 (m, 24 H), 3.5−3.6 (m, 1 H), 3.7−4.0 (m, 2 H), 4.2−4.5 (q, J = 1.8 Hz, 1 H), 5.26 (s, 1 H), 6.15 (s, 2 H), 6.87 (d, J = 7.7 Hz, 1 H), 7.3 (br s, 1 H); HRMS *m/z* 482.2474 (M^+).

***N*-Cyclohexyl-5-(3-methylbutyl)-6-oxo-5,6,7,8,9,10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo[1,2-*a*][1,4]diazepine-4-carboxamide 6f:** mp 152−154 °C; IR (KBr, cm^{-1}) ν 1625 (CO), 1690 (CO), 3420 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.6−2.0 (m, 18 H), 1.5 (s, 6 H), 2.3−3.0 (m, 4 H), 3.3−3.47 (m, 1 H), 5.07 (s, 1 H), 5.9−6.0 (m, 1 H), 6.23 (d, J = 7.8 Hz, 2 H), 6.88 (s, 1 H); HRMS *m/z* 458.2521 (M^+).

***N*-Cyclohexyl-5-cyclopentyl-6-oxo-5,6,7,8,9,10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo[1,2-*a*][1,4]diazepine-4-carboxamide 6g:** mp 192−194 °C; IR (KBr, cm^{-1}) ν 1620 (CO), 1680 (CO), 3410 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4): δ 1.1−2.0 (m, 26 H), 2.8−3.0 (m, 1 H), 3.47−3.59 (m, 1 H), 5.1 (s, 1 H), 5.7−5.9 (br s, 1 H), 6.16−6.3 (d, J = 7.6 Hz, 2 H), 6.9 (s, 1 H); HRMS *m/z* 466.2513 (M^+).

***N*-Cyclohexyl-5-(3-isopropoxypropyl)-6-oxo-5,6,7,8,9,10-hexahydro-4*H*-[1]benzothieno[3,2-*f*]pyrrolo[1,2-*a*][1,4]-diazepine-4-carboxamide 6h:** mp 117−119 °C; IR (KBr, cm^{-1}) ν 1635 (CO), 1660 (CO), 3320 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4): δ 1.1 (2s, 3 H), 1.04−2.1 (m, 24 H), 2.65−2.7 (m, 2 H), 3.25−3.32 (m, 2 H), 3.39−3.58 (m, 2 H), 3.5−3.61 (m, 1 H), 3.62−3.73 (m, 1 H), 5.12 (s, 1 H), 5.9−6.05 (br s, 1 H), 6.21−6.3 (d, J = 7.9 Hz, 2 H), 6.8 (s, 1 H, ArH); HRMS *m/z* 498.2763 (M^+).

8-Chloro-*N*-cycloheptyl-5-(4-methylbenzyl)-6-oxo-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-carboxamide 7a: mp 165−168 °C; IR (KBr, cm^{-1}) ν 1635 (CO), 1665 (CO), 3350 (NH); ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4): δ 0.75−1.6 (m, 12 H), 2.3 (s, 3 H), 3.3−3.48 (m, 1 H), 4.6−4.7 (q, J = 5.6 Hz, 2 H), 5.15 (s, 1 H), 5.9 (d, J = 2.2 Hz, 1 H), 6.0−6.08 (s, 1 H), 6.18−6.2 (s, 1 H), 7.0−7.4 (m, 7 H), 7.78 (d, J = 7.7 Hz, 1 H); HRMS *m/z* 476.2091 (M^+).

8-Chloro-*N*-cycloheptyl-5-benzyl-6-oxo-5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-carboxamide 7b: mp 124−127 °C; IR (KBr, cm^{-1}) ν 1630 (CO), 1670 (CO), 3330 (NH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ 0.73−1.58 (m, 12 H), 3.28−3.47 (m, 1 H), 4.61−4.72 (d, J = 5.9 Hz, 2 H), 4.8−4.96 (d, J = 5.9 Hz, 2 H), 5.12 (s, 1 H), 5.9−6.0 (m, 2 H, ArH), 6.18 (s, 1 H), 7.0−7.4 (m, 8 H), 7.77 (d, J = 7.8 Hz, 1 H); HRMS *m/z* 462.1935 (M^+).

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Supporting Information Available: Experimental procedures and characterization of **2a**−**c**, **3a**−**c**, and **4a**−**c** and ^{1}H and ^{13}C NMR spectral data for all final products **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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