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One-Step Assembly of Carbamoyl-Substituted Heteroannelated [1,4]Thiazepines

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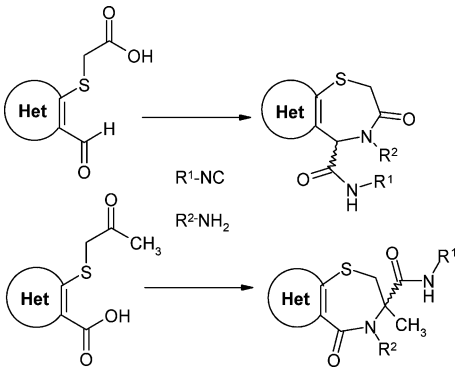

We present a convenient synthesis of novel heteroaryl-fused 3-oxo-1,4-thiazepine-5-carboxamides and 5-oxo-1,4-thiazepine-3-carboxamides using a modification of four-component Ugi condensation. We demonstrate the usefulness and versatility of the developed approach for the synthesis of variously substituted compounds and discuss the scope and limitations of the chemistry involved.

Introduction

The 1,4-thiazepine fragment is present in a wide number of natural and synthetic biologically active agents.[1] Among them, aryl- and heteroaryl-fused derivatives of this heterocycle represent an important group of compounds with interesting pharmaceutical properties.[2,3] In particular, different alkyl derivatives of 3,4-dihydro-5-oxo-1,4-benzothiazepine **I** (Figure 1) were described as calcium channel antagonists,[2a] HIV-1 enzyme integrase[2b] and reverse transcriptase[2c] inhibitors, and antitumor agents.[2d] Several heteroannelated bioisosteric analogues of this core fragment were described as potent inhibitors of Herpes simplex virus type 1 (HSV-1) replication (structure **II**),[3a] compounds possessing H1 antihistamine activity (structure **III**),[3b] selective antagonists of 5-HT_{1A} and dopamine D_2 receptors (structure **IV**),[3c] and vasoconstrictor agents (structure **V**).[3d] According to these examples, aryl-fused 1,4-thiazepines

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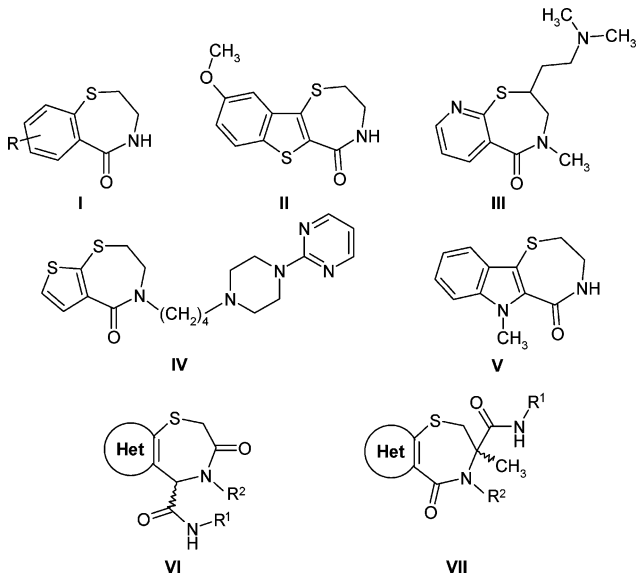

FIGURE 1. Biologically active molecules containing the aryl- and heteroaryl-fused 5-oxo-1,4-thiazepine moiety (structures **I**−**V**), and compounds synthesized in this work (structures **VI** and **VII**).

and their heterocyclic analogues represent promising synthetic targets. Development of efficient synthetic approaches to the related scaffolds may provide a valuable source of novel physiologically active agents.

In the reported synthetic approaches to the aryl- and heteroaryl-fused derivatives of 3(5)-oxo-1,4-thiazepine, a key reaction is the intramolecular cyclization of the appropriate aryl/heteroaryl derivatives leading to the desired molecules.[2d,4] For example, 5-oxo-1,4-thiazepino[6,7-*b*]indole was synthesized using intramolecular amide bond formation in 3-[(2-aminoethyl)-thio]-1*H*-indole-2-carboxylate in the presence of sodium ethylate.[4a] Similar scheme was used for assembly of benzothieno[2,3-*f*]-1,4-thiazepin-5(2*H*)-one **II**.[4d] However, the described synthetic strategies have found limitations mainly due to lack of versatility and a limited number of the appropriate initial reactants. In addition, these approaches have not provided a robust method suitable for the production of combinatorial libraries.

Multiple component condensations (MCCs) are of great value for the contemporary organic and medicinal chemistry because large arrays of compounds with diverse substitution patterns can be prepared in one step under mild reaction conditions. A classical example of MCC is 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.[5] One important modification of this reaction is the use of bifunctional reagents (BFRs).[6−8] For example, a series of 2,3-dihydro-1*H*-isoindol-3-ones was prepared from 2-formylbenzoic acid.[6a] Using 1,8-naphthalaldehydic acid, 2-formylphenoxyacetic acid, and 2′-formylphenoxy-2-benzoic acid as the BFRs in Ugi coupling, a series of rare 6-, 7- and 8-membered heterocyclic rings was obtained.[6a] Reaction of ω-ketoacids[6b] or aldehyde acids[6c] with the corresponding isonitriles and amines led to β-lactams. Several model 1,4-benzothiazepin-5-ones were synthesized starting from the corresponding thiacarboxylic keto acids, amines, and isocyanides.[7] Recently, we developed a modified variant of the classical Ugi reaction, in which heterocyclic keto acids were used as the bifunctional coupling components for the synthesis of rare heterocyclic structures.[8] Using this method, we efficiently synthesized several series of novel pyrrolo[1,2-*a*][1,4]diazepines,[8a] 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones, and 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones.[8b] In this work, we have focused on broadening the scope of this useful synthetic methodology. Specifically, we describe an efficient route to novel heteroaryl-fused carboxamide derivatives of 3-oxo-1,4-thiazepine **VI** and 5-oxo-1,4-thiazepine **VII** (Figure 1) heterocycles, which were not previously reported in the literature.

Results and Discussion

In the first part of our work, we synthesized four series of novel heteroaryl-fused 3-oxo-1,4-thiazepine-5-carboxamides of general structure **VI** (Figure 1). The bifunctional reagents for Ugi condensation **3a**−**d** were obtained using a modified approach by Cagniant et al.[9] (Scheme 1).

The initial formyl chlorides **1a**−**d**, obtained following known approaches,[10−13] were converted to the corresponding BFRs **3a**−**d** using two synthetic methods. According to method A, the methyl carboxylates **2a**,**b** were initially synthesized in moderate yields (38% and 56%, respectively) from **1a**,**b** by using the reaction with methyl mercaptoacetate in the presence of K_2CO_3 in DMF. Esters **2a**,**b** were then smoothly hydrolyzed by aqueous alkali to furnish the desired aldehyde acids **3a** and **3b** (yields 86 and 85%, respectively). The relatively low overall yields of the desired BFRs achieved in these reaction sequences prompted us to explore an alternative synthetic route. We have found that reaction of **1a**−**d** with disodium mercaptoacetate in methanol (method B) led to the desired heterocycles **3a**−**d** in 45−70% yield. Due to better overall yields and a shortened synthetic procedure, route B can be recommended as method of choice for the synthesis of **3a**−**d**.

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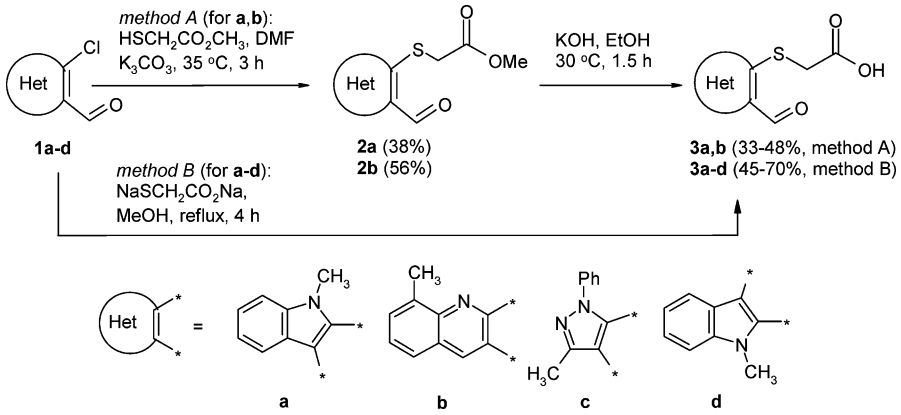
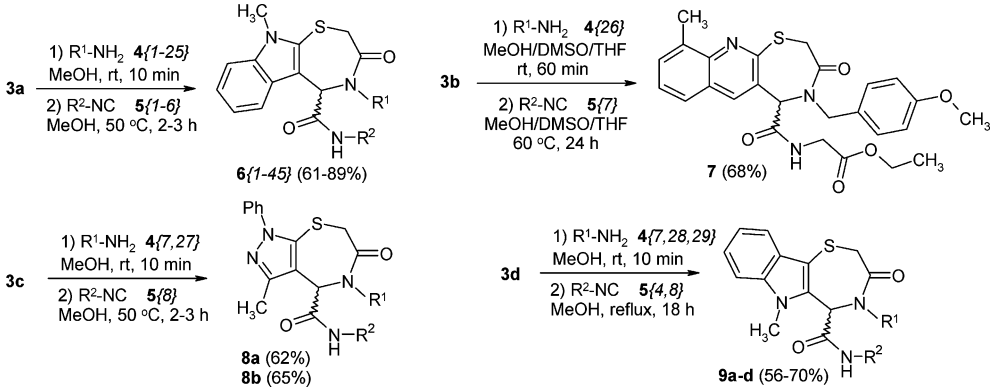
SCHEME 1. Synthesis of Bifunctional Reagents 3a−d



SCHEME 2. Synthesis of Heteroaryl-Fused 3-Oxo-1,4-thiazepine-5-carboxamides

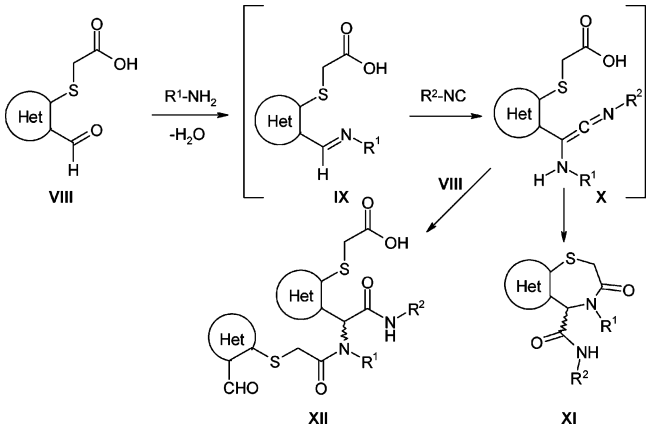


We have found that reaction of aldehyde acids **3a**−**d** with various amines **4**{*1*−*33*} and isocyanides **5**{*1*−*9*} in methanol led to novel heteroaryl-fused derivatives of 3-oxo-1,4-thiazepine-5-carboxamides **6**{*1*−*45*}, **7**, **8a**,**b**, and **9a**−**d** in moderate to good yield (Scheme 2). The reaction yields were found to be sensitive to the order in which the amine and isonitrile components were added to the initial aldehyde acids. In an optimized experimental protocol, the equimolar amounts of aldehyde acid and primary amine were dissolved in an appropriate solvent (or solvent mixture), and the mixture was kept at room temperature for 10−60 min until the complete conversion of the BFR. Then the equimolar amount of isocyanide was added, and the resulting mixture was heated for 1−24 h, depending on the nature of reactants.

The described reactions presumably follow the same initial mechanism as the classical Ugi condensation (Scheme 3). The initial step is the formation of a Schiff base as a result of reaction of the aldehyde **VIII** with the primary amine. The resulting imine **IX** is then attacked by the isonitrile to give an iminovinyl intermediate **X**. The latter then reacts intramolecularly with the carboxylic group, and the acylation product undergoes recyclization leading to the final thiazepine **XI**. When unreacted aldehyde acid is present in the reaction mixture, there is the possibility of an intermolecular interaction between the intermediate **X** and the second molecule of acid **VIII** leading to a standard Ugi 4CC product **XII**. The process is controlled kinetically, and the overall yield of the desired thiazepines depends on the relative rate constants at each step.

For example, in the case of [(3-formyl-8-methylquinolin-2-yl)thio]acetic acid **3b**, simultaneous addition of isonitrile and amine to the initial BFR led to a significant amount of the

SCHEME 3. Mechanism of Formation of the Desired Thiazepines and the Side Products



unwanted side product corresponding to structure **XII** in Scheme 3. According to LC/MS analysis of the reaction mixture, its relative amount exceeded 35% of the desired compound. As a result, the yield of the purified diazepine **7** was significantly decreased (up to 20−30%). To prevent the possibility of this side reaction, we used a modified protocol for this condensation. At the first step, aldehyde acid **3b** was reacted with primary amine at room temperature for 1 h. After the complete conversion of **3b**, isonitrile was added, and the resulting mixture was stirred at 60 °C for 24 h. Due to this modification, the yield of the desired compound was increased up to 68%.

Similar modification allowed us to optimize the reaction conditions and improve the yields of all other cyclization products depicted in Scheme 2. Although LC/MS analysis of

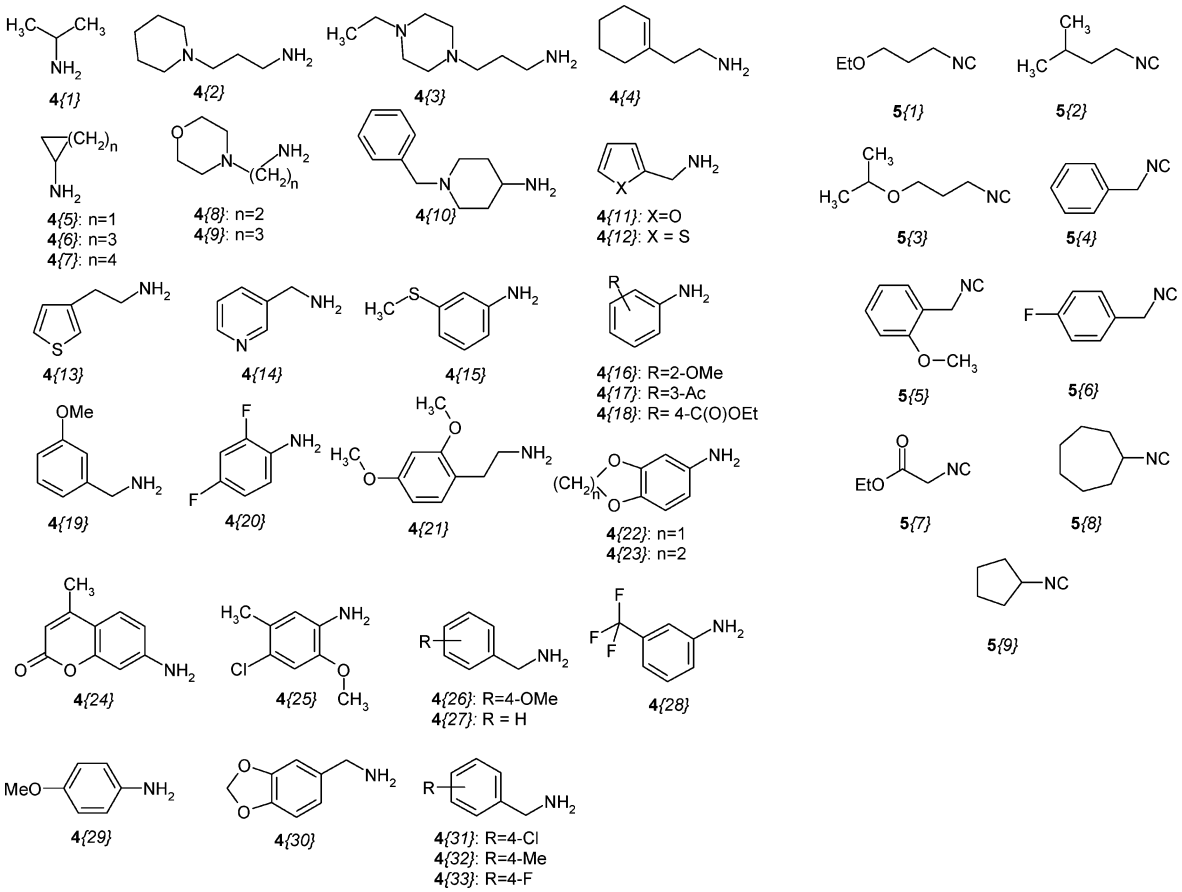


FIGURE 2. Amines **4**{*1*−*33*} and isonitriles **5**{*1*−*9*} used in this work.

the reaction mixtures still shows the presence of such side products corresponding to structure **XII** in Scheme 3, their relative amount did not exceed 3−5% of the desired product for most of the studied reactions.

Typically, the full conversion of initial aldehyde acids was achieved within 1−24 h, depending primarily on both the nature of the heterocyclic BFR and the amine component. With respect to amine reagent, various cycloaliphatic and aromatic primary amines, such as substituted anilines, benzyl and phenylamines, and linear and branched aliphatic amines, were well tolerated (Figure 2). Somewhat surprisingly, even aromatic anilines with electron-withdrawing groups, such as 3-CF_3-$C_6H_4NH_2$, readily reacted in this condensation, though after more prolonged heating as compared to more nucleophilic amines. A restriction is the limited number of commercially or synthetically available isonitriles. In this work, we used nine different isonitriles **5**{*1*−*9*} available from commercial sources (Figure 2).

Structures and yields of the representative condensation products are shown in Table 1.

For assembly of the aryl-fused 5-oxo-1,4-thiazepine-3-carboxamide heterocyclic system (structure **VII**, Figure 1), we explored the possibility of use of ketoacid **11** as an alternative BFR in the reaction with isonitriles and primary amines (Scheme 4). A similar scheme was reported by Marcaccini et al. for the synthesis of a series of 1,4-benzothiazepin-5-ones.[7]

Compound **10** was prepared as reported by Blank et al.[14] The reaction of mercapto acid **10** with 1-bromoacetone in the presence of Na_2CO_3 in water led to ketoacid **11** in a good yield (80%). The desired thiazepino[6,7-*b*]indoles **12a**−**e** were then synthesized by the reaction with benzylamines **4**{*27*, *30*−*33*} and cyclopentylisocyanide **5**{*9*} in methanol at room temperature (yield 64−75%). Of note, the reaction yields in this case were found to be independent of the order in which the amine and isonitrile components were added to the initial keto acid. Structures and yields of the synthesized compounds from this series are shown in Table 2.

In both condensation variants, the desired products usually precipitated from the reaction mixtures after the reaction was cooled to room temperature. All compounds were obtained as racemic mixtures. The assignment of these structures was made on the basis of ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectroscopy data. In many cases, pure crystalline substances could be obtained, thus allowing analysis of the individual compounds through X-ray crystallography.

In summary, we have shown that carboxamide derivatives of heteroaryl-fused 5(3)-oxo-1,4-thiazepine can be efficiently prepared by a novel modification of four-component Ugi reaction of bifunctional aldehyde/keto 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 thiazepines. 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

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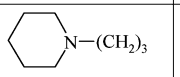
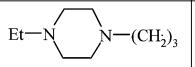
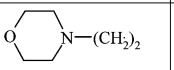
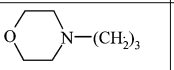
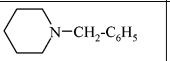
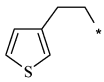
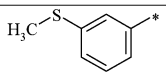
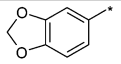
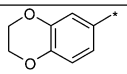
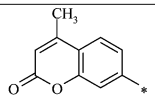
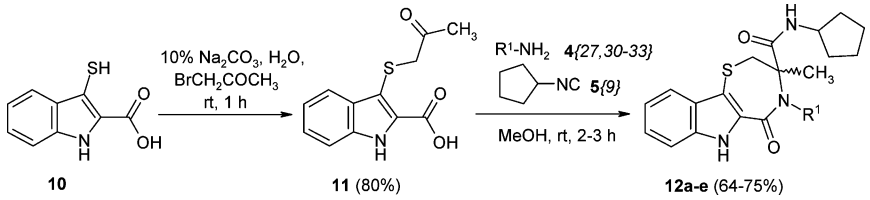
TABLE 1. Structures and Yields of Representative Compounds 6{*1*−*45*}, 7, 8a,b, and 9a−d

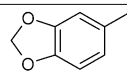
№	R^1	R^2	Yield,%
6{*1*}	*i*-Pr	EtO-$(CH_2)_3$	66
6{*2*}		*i*-PrO$(CH_2)_3$	71
6{*3*}		*i*-PrO$(CH_2)_3$	73
6{*4*}	2-cyclohex-1-en-1-ylethyl	Bn	69
6{*5*}	*c*-Pr	EtO-$(CH_2)_3$	59
6{*6*}	*c*-C_5H_9	4-F-C_6H_4-CH_2	68
6{*7*}	*c*-C_6H_{11}	4-F-C_6H_4-CH_2	79
6{*8*}		Bn	70
6{*9*}		EtO-$(CH_2)_3$	74
6{*10*}		EtO-$(CH_2)_3$	62
6{*11*}		EtO-$(CH_2)_3$	68
6{*12*}		EtO-$(CH_2)_3$	70
6{*13*}		EtO-$(CH_2)_3$	62
6{*14*}		EtO-$(CH_2)_3$	69
6{*15*}		3-methylbutyl	75
6{*16*}	2-OMe-C_6H_4	2-OMe-Bn	80
6{*17*}	3-Ac-C_6H_4	EtO-$(CH_2)_3$	56
6{*18*}	4-EtOC(O)-C_6H_4	4-F-C_6H_4-CH_2	71
6{*19*}	3-MeO-C_6H_4-CH_2	EtO-$(CH_2)_3$	64
6{*20*}	2,4-di-F-C_6H_3	EtO-$(CH_2)_3$	72
6{*21*}	2,4-di-MeO-C_6H_4-$(CH_2)_2$	4-F-C_6H_4-CH_2	61
6{*22*}		EtO-$(CH_2)_3$	64
6{*23*}		3-methylbutyl	68
6{*24*}		Bn	73
6{*25*}	2-MeO-4-Cl-5-Me-C_6H_2	Bn	69
7	4-MeO-C_6H_4-CH_2	EtOC(O)-CH_2	68
8a	*c*-C_6H_{11}	*c*-C_7H_{13}	62
8b	Bn	*c*-C_7H_{13}	65
9a	3-CF_3-C_6H_4	*c*-C_7H_{13}	70
9b	*c*-C_6H_{11}	*c*-C_7H_{13}	76
9c	4-MeO-C_6H_4	Bn	64
9d	3-CF_3-C_6H_4	Bn	56

SCHEME 4. Synthesis of Heteroaryl-Fused 5-Oxo-1,4-thiazepine-3-carboxamides 12a−e



obtained compounds represent valuable starting points for the development of compounds of biological interest. The use of compounds from series **6**−**9** and **12** in the search for novel bioactive agents is under investigation by the ChemDiv Co. and will be reported in due course.

TABLE 2. Structures and Yields of Compounds 12a−e

№	R^1	Yield,%
12a		68
12b	4-Cl-C_6H_4-CH_2	64
12c	4-Me-C_6H_4-CH_2	75
12d	4-F-C_6H_4-CH_2	58
12e	Bn	63

Experimental Section

(3-Formyl-1-methyl-1*H*-indol-2-ylsulfanyl)acetic Acid 3a. K_2CO_3 (8.8 g, 0.064 mol) was added to a solution of 2 chloro-1-methyl-1*H*-indolcarbaldehyde (8.8 g, 0.064 mol) in DMF (50 mL) followed by a dropwise addition of methyl mercaptoacetate (6.4 g, 0.060 mol). The mixture was stirred at 35 °C for 3 h, and then water (100 mL) was added. The mixture was extracted with benzene, the combined extracts were dried over $CaCl_2$, and the solvent was removed in vacuo. The crude residue was triturated in hexane, and the resulting precipitate was filtered off and dried to afford 5.4 g (38%) of **2a** (mp 74−76 °C), which was used at the

next step without further purification. KOH (0.042 mol) was added dropwise to a solution of **2a** (0.021 mol) in ethanol (50 mL). The reaction mixture was stirred at 30 °C for 1.5 h and then treated with water (50 mL) and acidified with concd HCl until pH 2 was reached. The formed precipitate was filtered off and dried in vacuo. Recrystallization from benzene/acetonitrile mixture gave 4.1 g (82%) of **3a**. Mp: 182−184 °C. ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 2 H), 3.92 (s, 3 H), 7.29 (t, J_a = 7.55 Hz, J_b = 8.0 Hz, 1 H), 7.36 (t, J_a = 8.35 Hz, J_b = 7.55 Hz, 1 H), 7.64 (d, J = 8.35 Hz, 1 H), 8.15 (d, J = 8.0 Hz, 1 H), 10.18 (s, 1 H), 12.85 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ 178.0, 172.7, 164.9, 133.3, 124.3, 122.3, 120.6, 116.9, 110.8, 107.0, 35.3, 31.4. Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.65; H, 4.37; N, 5.79.

(3-Formyl-8-methylquinolin-2-ylsulfanyl)acetic Acid 3b. This compound was obtained in 48% overall yield from **1b** by the same procedure described for **3a**. Mp: 185−187 °C. ^{1}H NMR (DMSO-d_6): δ 10.25 (s, 1 H), 8.78 (s, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 7.2 Hz, 1 H), 7.43 (t, J = 7.5 Hz, 1 H), 4.00 (s, 2 H), 2.60 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ 192.3, 170.9, 156.3, 147.7, 146.7, 136.2, 134.0, 127.9, 127.1, 126.8, 124.8, 32.9, 18.0.

(4-Formyl-2-methyl-2*H*-pyrazol-3-ylsulfanyl)acetic Acid 3c. NaOH (10.9 g, 0.37 mol) was added to a solution of thioglycolic acid (11.4 g, 0.12 mol) in absolute ethanol (45 mL). The reaction mixture was stirred at 40−50 °C for 2 h and then cooled to rt. The formed precipitate was filtered off, washed with absolute ethanol, and dried to yield 12.4 g (74%) of disodium mercaptoacetate. This compound was added to a solution of chloride **1c** (16 g, 0.08 mol) in MeOH (160 μL). The reaction mixture was heated at reflux for 4 h and then cooled to rt. Water (100 mL) was added, and the resulting mixture was acidified with aqueous HCl until pH 2 was reached and then stirred at rt overnight. The formed precipitate was filtered off, washed thoroughly with water, and dried to afford **3c** as colorless crystals. Mp: 63−65 °C. Yield: 70%. ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3 H), 3.54 (s, 2 H), 7.47−7.64 (m, 5 H), 10.03 (s, 1 H), 12.83 (br.s, 1 H). ^{13}C NMR (DMSO-d_6): δ 180.1, 171.4, 150.3,146.9, 142.3, 131.5, 128.0, 124.4, 121,0 38.4, 13.0. Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.54; H, 4.25; N, 10.49.

(2-Formyl-1-methyl-1*H*-indol-3-ylsulfanyl)acetic Acid 3d. This compound was obtained in 45% yield by the same procedure described for **3c**. Mp: 156−158 °C. ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 2 H), 3.92 (s, 3 H), 7.29 (t, J_a = 7.55 Hz, J_b = 8.0 Hz, 1 H), 7.36 (t, J_a = 8.35 Hz, J_b = 7.55 Hz, 1 H), 7.64 (d, J = 8.35 Hz, 1 H), 8.15 (d, J = 8.0 Hz, 1 H), 10.18 (s, 1 H), 12.85 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ 181.6, 170.3, 138.6, 134.0, 125.1, 122.4, 121.8, 118.7, 115.3, 111.0, 38.8, 31.1. Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.6. Found: C, 57.68; H, 4.39; N, 5.72.

The same synthetic procedure described for **3c**,**d** can be used for the synthesis of **3a**,**b** (yields 56% and 65%, respectively).

General Procedure for Preparation of 10-Methyl-3-oxo-3,4,5,-10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamides 6{*1*−*45*}. The aldehyde acid **3a** (0.5 mmol) and the corresponding primary amine (0.5 mmol) were dissolved in methanol (3 mL). The solution was kept for 10 min at rt, the isonitrile **5**{*1*−*6*} (0.5 mmol) was added, and the resulting mixture was stirred at 50 °C for 2−3 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). On completion, the reaction mixture was cooled to rt, and the formed precipitate was filtered off, washed with methanol, and purified by recrystallization from diethyl ether of by chromatography on silica gel, eluting with CH_2Cl_2. The title compounds were obtained as colorless solids in moderate to good yields (61−89%).

Representative spectral data for compounds ***6***{*1*−*45*}:

***N*-(3-Ethoxypropyl)-4-isopropyl-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*1*}.** Yield: 66%. ^{1}H NMR (DMSO-d_6): δ 7.78 (d, J = 7.5 Hz, 1 H), 7.41 (d, J = 7.5 Hz, 1 H), 7.40 (br s, 1 H), 7.13 (t, J = 7.5 Hz, 1 H), 7.07 (t, J = 7.5 Hz, 1 H), 5.31 (s, 1 H), 4.76 (sept, J = 6.6 Hz, 1 H), 4.21 (d, J = 13.9 Hz,. 1 H), 3.62 (s, 3 H), 3.50 (d, J = 13.9 Hz, 1 H), 3.31 − 3.03 (m, 6 H), 1.59−1.45 (m, 2 H), 1.23 (d, J = 7.0 Hz, 3 H), 0.94 (t, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 170.2, 167.8, 136.3, 131.5, 127.2, 120.8, 119.6, 116.4, 108.9, 105.2, 67.7, 65.2, 51.6, 45.4, 37.3, 32.0, 29.8, 28.8, 19.9, 19.3, 14.8. HRMS: *m*/*z* 404.2002 (M^+). Anal. Calcd for $C_{21}H_{29}N_3O_3S$: C, 62.50; H, 7.24; N, 10.41. Found: C, 62.58; H, 7.29; N, 10.67.

***N*-(3-Isopropoxypropyl)-10-methyl-3-oxo-4-(3-piperidin-1-yl-propyl)-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*2*}.** Yield: 71%. ^{1}H NMR (DMSO-d_6): δ 7.65 (t, J = 5.7 Hz, 1 H), 7.62 (d, J = 7.9 Hz, 1 H), 7.41 (d, J = 7.9 Hz, 1 H), 7.13 (t, J = 7.9 Hz, 1 H), 7.06 (t, J = 7.9 Hz, 1 H), 5.49 (s, 1 H), 4.38 (d, J = 13.8 Hz, 1 H), 3.87−3.73 (m, 1 H), 3.62 (s, 3 H), 3.47 (d, J = 13.8 Hz, 1 H), 3.43−3.21 (m, 4 H), 3.19−3.09 (m, 2 H), 2.31−1.93 (br m, 6 H), 1.66−1.43 (m, 4 H), 1.43−1.20 (br m, 6 H), 0.96 (d, J = 5.8 Hz, 3 H), 0.96 (d, J = 5.8 Hz, 3 H), 0.94 (d, J = 5.8 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 169.9, 168.6, 136.3, 131.7, 127.5, 120.9, 119.5, 116.5, 108.8, 104.6, 70.5 (2C), 65.0, 58.4, 55.2, 53.5 (2C), 47.4, 37.0, 31.9, 29.8, 29.3, 25.0, 24.7, 23.7, 21.8 (2C). HRMS: *m*/*z* 501.2903 (M^+). Anal. Calcd for $C_{27}H_{40}N_4O_3S$: C, 64.77; H, 8.05; N, 11.19. Found: C, 64.85; H, 8.18; N, 11.02. Crystallographic data: monoclinic single crystal (0.40 × 0.15 × 0.05 mm^3), space group *P*21/*n*, unit cell constants a = 12.252(4) Å, b = 13.211(4) Å, c, 17.676(5) Å, α = 90°, β = 102.16(2)°, γ = 90°, V = 2796.9(15) Å^3, Z = 4, D_x = 1.189 Mg/m^3. The final R indices are R1 = 0.0467, wR2 = 0.0835.

***N*-Benzyl-4-(2-cyclohex-1-en-1-ylethyl)-10-methyl-3-oxo-3,4,5,-10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6-{*4*}.** Yield: 69%. ^{1}H NMR (DMSO-d_6): δ 8.35 (t, J = 5.8 Hz, 1 H), 7.65 (d, J = 7.5 Hz, 1 H), 7.42 (d, J = 7.5 Hz, 1 H), 7.34−7.17 (m, 5 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.06 (t, J = 7.5 Hz, 1 H), 5.53 (s, 1 H), 4.78 (br s, 1 H), 4.43 (d, J = 13.8 Hz, 1 H), 4.34 (dd, J = 14.9, 5.8 Hz 1 H), 4.24 (dd, J = 14.9, 5.8 Hz, 1 H), 4.08−3.89 (m, 1 H), 3.61 (s, 3 H), 3.39 (d, J = 13.8 Hz, 1 H), 3.24−3.14 (m, 1 H), 2.09−1.05 (m, 10 H). ^{13}C NMR (DMSO-d_6): δ 170.3, 168.5, 139.1, 136.2, 133.8, 132.1, 128.2 (2C), 127.7, 127.2 (2C), 126.8, 122.3, 120.8, 119.4, 116.6, 108.6, 104.7, 58.4, 47.7, 42.8, 35.7, 32.0, 29.8, 27.4, 24.5, 22.2, 21.6. HRMS: *m*/*z* 474.2218 (M^+). Anal. Calcd for $C_{28}H_{31}N_3O_2S$: C, 71.01; H, 6.60; N, 8.87. Found: C, 71.54; H, 6.49; N, 8.67.

4-Cyclopropyl-*N*-(3-ethoxypropyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*5*}. Yield: 59%. ^{1}H NMR (DMSO-d_6): δ 7.62 (d, J = 7.5 Hz, 1 H), 7.42 (d, J = 7.5 Hz, 1 H), 7.44 (t, J = 5.5 Hz, 1 H), 7.14 (t, J = 7.5 Hz, 1 H), 7.07 (t, J = 7.5 Hz, 1 H), 5.40 (s, 1 H), 4.13 (d, J = 13.9 Hz, 1 H), 3.62 (s, 3 H), 3.48 (d, J = 13.9 Hz, 1 H), 3.31−3.18 (m, 4 H), 3.14 (q, J = 6.2 Hz, 1 H), 2.88−2.79 (m, 1 H), 1.59 (q, J = 6.2 Hz, 2 H), 0.95 (t, J = 7.0 Hz, 3 H), 0.86−0.66 (m, 2 H), 0.66−0.54 (m, 1 H), 0.45−0.32 (m, 1 H). ^{13}C NMR (DMSO-d_6): δ 170.3, 170.0 136.3, 131.6, 127.3, 121.0, 119.7, 116.2, 109.0, 104.5, 67.6, 65.2, 59.9, 37.2, 33.2, 32.6, 29.8, 28.9, 14.8, 8.8, 7.2. HRMS: *m*/*z* 402.1850 (M^+). Anal. Calcd for $C_{21}H_{27}N_3O_3S$: C, 62.82; H, 6.78; N, 10.46. Found: C, 62.66; H, 6.57; N, 10.74.

4-Cyclopentyl-*N*-(4-fluorobenzyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*6*}. Yield: 68%. ^{1}H NMR (DMSO-d_6): δ 8.05 (t, J = 6.0 Hz, 1 H), 7.73 (d, J = 8.1 Hz, 1 H), 7.43 (d, J = 8.1 Hz, 1 H), 7.30−7.20 (m, 2 H), 7.18−7.01 (m, 4 H), 5.28 (s, 1 H), 4.89 (d, J = 8.3 Hz, 1 H), 4.22 (d, J = 6.0 Hz, 2 H), 3.97 (d, J = 13.9 Hz, 1 H), 3.62 (s, 3 H), 3.43 (J = 13.9 Hz, 1 H), 3.62 (s, 3 H), 3.43 (J = 13.9 Hz, 1 H), 1.97−1.28 (m, 7 H), 1.18−0.95 (m, 1 H). ^{13}C NMR (DMSO-d_6): δ 170.4, 167.8, 161.1, 135.9 (2C), 131.7, 129.3, 129.2, 127.4, 120.8, 119.7, 116.2, 115.0, 114.7, 108.9, 104.9, 55.4, 52.7, 42.4, 31.6, 29.9, 28.8, 28.2, 23.8, 23.6. HRMS: *m*/*z* 452.1808 (M^+). Anal. Calcd for $C_{23}H_{22}FN_3O_2S$: C, 65.23; H, 5.24; N, 9.92. Found: C, 65.39; H, 5.09; N, 10.12.

4-Cyclohexyl-*N*-(4-fluorobenzyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*7*}. Yield: 79%. ^{1}H NMR (DMSO-d_6): δ 8.04 (t, J = 6.9 Hz, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 1 H), 7.31−7.18 (m, 2 H), 7.17−6.98 (m, 4 H), 5.42 (s, 1 H), 4.44−4.29 (br m, 1 H), 4.31−4.13−4.03 (m, 2 H), 4.08 (d, J = 13.9 Hz, 1 H), 3.61 (s, 3 H), 3.44 (d, J = 13.9 Hz, 1 H), 1.86−1.42 (m, 5 H), 1.42−0.96 (m, 5 H). ^{13}C NMR (DMSO-d_6): δ 170.5, 167.8, 161.1, 135.8 (2C), 131.6, 129.3, 129.2, 127.4, 120.7, 119.6, 116.5, 115.0, 114.7, 108.9, 105.2, 53.8, 52.4, 42.3, 31.9, 30.1, 29.8, 29.3, 25.2, 25.3, 24.7. HRMS: *m*/*z* 466.1956 (M^+). Anal. Calcd for $C_{26}H_{28}FN_3O_2S$: C, 67.07; H, 6.06; N, 9.03. Found: C, 67.21% H, 6.16; N, 9.15.

4-(1-Benzylpiperidin-4-yl)-*N*-(3-ethoxypropyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*10*}. Yield: 62%. ^{1}H NMR (DMSO-d_6): δ 7.81 (d, J = 7.3 Hz, 1 H), 7.46−7.37 (m, 2 H), 7.36−7.18 (m, 5 H), 7.17−7.04 (m, 2 H), 5.35 (s, 1 H), 4.37−4.23 (m, 1 H), 4.27 (d, J = 13.9 Hz, 1 H), 3.60 (s, 3 H), 3.52 (d, J = 13.9 Hz, 1 H), 3.43 (s, 2 H), 3.30−3.16 (m, 4 H), 3.12−2.91 (m, 2 H), 2.95−2.85 (m, 1 H), 2.75−2.64 (m, 1 H), 2.07−1.83 (m, 3 H), 1.76−1.29 (m, 4 H), 1.20−1.05 (m, 1 H), 0.94 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 170.1, 168.4, 138.2, 136.2, 131.7, 128.7 (2C), 128.0 (2C), 127.2, 126.8, 120.9, 119.7, 116.5, 108.9, 105.0, 67.6, 65.1, 61.8, 52.7, 52.5, 52.4, 37.3, 32.1 (2C), 29.8, 29.3, 28.8, 28.6, 14.8. HRMS: *m*/*z* 535.2742 (M^+). Anal. Calcd for $C_{30}H_{38}N_4O_3S$: C, 67.39; H, 7.16; N, 10.48. Found: C, 67.53; H, 7.29; N, 10.44.

***N*-(3-Ethoxypropyl)-4-(2-furylmethyl)-10-methyl-3-oxo-3,4,5,-10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6-{*11*}.** Yield: 68%. ^{1}H NMR (DMSO-d_6): δ 7.72 (t, J = 5.5 Hz, 1 H), 7.47 (d, J = 7.9 Hz, 1 H), 7.39−7.25 (m, 2 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.03 (t, J = 7.9 Hz, 1 H), 6.19 (dd, J = 3.2, 2.0, Hz, 1 H), 6.13 (d, J = 3.2 Hz, 1 H), 5.55 (s, 1 H), 5.09 (d, J = 15.6 Hz, 1 H), 4.53 (d, J = 13.8 Hz, 1 H), 4.40 (d, J = 15.6 Hz, 1 H), 3.62 (s, 3 H), 3.57 (d, J = 13.8 Hz, 1 H), 3.28−3.15 (m, 4 H), 3.13 (q, J = 6.4 Hz, 2 H), 1.60 (q, J = 6.4 Hz, 2 H), 0.99 (t, J = 6.8 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 169.7, 169.1, 150.6, 142.4, 136.2, 131.6, 127.3, 120.9, 119.4, 116.5, 110.3, 108.9, 107.8, 104.4, 67.5, 65.2, 58.1, 45.5, 37.0, 32.1, 29.9, 28.9, 14.9. HRMS: *m*/*z* 442.1799 (M^+). Anal. Calcd for $C_{23}H_{27}N_3O_4S$: C, 62.56; H, 6.16; N, 9.52. Found: C, 62.46; H, 5.84; N, 9.71.

***N*-(3-Ethoxypropyl)-10-methyl-3-oxo-4-(2-thien-3-ylethyl)-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*13*}.** Yield: 62%. ^{1}H NMR (DMSO-d_6): δ 7.69 (t, J = 5.5 Hz, 1 H), 7.65 (d, J = 7.7 Hz, 1 H), 7.42 (d, J = 7.7 Hz, 1 H), 7.31−7.25 (m, 1 H), 7.13 (t, J = 7.7 Hz, 1 H), 7.07 (t, J = 7.7 Hz, 1 H), 6.97−6.77 (m, 1 H), 6.88 (d, J = 4.9 Hz, 1 H), 5.60 (s, 1 H), 4.40 (d, J = 13.6 Hz, 1 H), 4.06−3.91 (m, 1 H), 3.62 (s, 3 H), 3.60−3.46 (m, 1 H), 3.48 (d, J = 13.6 Hz, 1 H), 3.33−3.20 (m, 4 H), 3.20−3.09 (m, 2 H), 2.67−2.55 (m, 2 H), 1.61−1.51 (m, 2 H), 0.97 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (DMSO-d$_6$): δ 170.0, 168.5, 138.8, 136.2, 131.8, 128.2, 127.5, 125.5, 121.0, 120.9, 119.5, 116.5, 198.8, 104.6, 67.5, 65.2, 58.4, 49.8, 37.0, 31.9, 29.8, 28.9, 28.0, 14.8. HRMS: *m*/*z* 472.1722 (M^+). Anal. Calcd for $C_{24}H_{29}N_3O_3S_2$: C, 61.12; H, 6.20; N, 8.91. Found: C, 61.07; H, 6.03; N, 8.72.

***N*-(3-Ethoxypropyl)-10-methyl-3-oxo-4-(pyridin-3-ylmethyl)-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*14*}.** Yield: 69%. ^{1}H NMR (DMSO-d_6): δ 8.39 (d, J = Hz 1.5, 1 H), 8.28 (dd, J = 4.7, 1.5 Hz, 1 H), 7.76 (t, J = 5.5 Hz, 1 H), 7.55 (dt, J = 7.9, 1.9 Hz, 1 H), 7.48 (d, J = 7.9 Hz, 1 H), 7.38 (d, J = 7.9 Hz, 1 H), 7.15 (dd, J = 7.9, 4.9, 1 H), 7.10 (t, J = 7.9 Hz, J = 4.9 Hz, 1 H), 7.00 (t, J = 7.9 Hz, 1 H), 5.59 (s, 1 H), 5.13 (d, J = 15.6 Hz, 1 H), 4.58 (d, J = 13.8 Hz, 1 H), 4.46 (d, J = 15.6 Hz, 1 H), 3.63 (s, 3 H), 3.61 (d, 13.8 Hz,1 H), 3.26 (q, J = 7.0 Hz, 4 H),3.14 (q, J = 6.4 Hz, 2 H), 1.59 (q, J = 6.4 Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ 169.7, 169.6, 148.5, 148.0, 136.2, 134.8, 133.2, 131.8, 127.2, 123.1, 121.0, 119.4, 116.5, 198.9, 104.3, 67.4, 65.2, 59.1, 50.6, 37.0, 32.2, 30.0, 28.9, 14.9. HRMS: *m*/*z* 453.1953 (M^+). Anal. Calcd for $C_{24}H_{28}N_4O_3S$: C, 63.69; H, 6.24; N, 12.38. Found: C, 63.76; H, 6.34; N, 12.46.

4-(3-Acetylphenyl)-*N*-(3-ethoxypropyl)-10-methyl-3-oxo-3,4,5,-10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6-{*17*}. Yield: 56%. ^{1}H NMR (DMSO-d_6): δ 7.88 (d, J = 7.3 Hz, 1 H), 7.75 (s, 1 H), 7.63−7.49 (m, 3 H), 7.46−7.33 (m, 2 H), 7.14 (t, J = 7.3 Hz, 1 H), 7.02 (t, J = 7.3 Hz, 1 H), 5.74 (s, 1 H), 4.49 (d, J = 13.9 Hz, 1 H), 3.72 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.30−3.11 (m, 4 H), 2.53 (s, 3 H), 1.62−1.55 (m, 2 H), 0.94 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 197.2, 169.6, 168.9, 144.6, 137.6, 136.4, 131.9, 131.3, 129.4, 127.4, 126.8, 125.9, 121.2, 119.7, 116.5, 109.1, 103.7, 67.6, 65.2, 61.6, 37.4, 32.4, 30.0, 28.9, 26.7, 14.8. HRMS: *m*/*z* 480.1951 (M^+). Anal. Calcd for $C_{26}H_{29}N_3O_4S$: C, 65.11; H, 6.09; N, 8.76. Found: C, 64.98; H, 6.27; N, 8.92.

Ethyl 4-(5-{[(4-Fluorobenzyl)amino]carbonyl}-10-methyl-3-oxo-2,3,5,10-tetrahydro-4*H*-[1,4]thiazepino[7,6-*b*]indol-4-yl)benzoate 6{*18*}. Yield: 71%. ^{1}H NMR (DMSO-d_6): δ 8.19 (t, J = 6.0 Hz, 1 H), 7.95 (d, J = 8.5 Hz, 2 H), 7.62 (d, J = 7.9 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H), 7.37 (d, J = 8.5 Hz, 2 H), 7.28−7.16 (m, 2 H), 7.19−6.97 (m, 4 H), 5.88 (s, 1 H), 4,34 (d, J = 13.8 Hz, 1 H), 4.40−4.17 (m, 4 H), 3.69 (s, 3 H), 3.66 (d, J = 13.8 Hz, 1 H), 1.30 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 169.8, 168.4, 165.1, 161.1, 148.2, 135,9 (2C), 135.2, 129.9 (2C), 129.3, 129.2, 127.9, 127.5, 126.7 (2C), 121.1, 119.8, 116.5, 115.0, 114.7, 109.1, 103.6, 61.3, 60.7, 42.4, 32.2, 30.0, 14.1. HRMS: *m*/*z* 532.1702 (M^+). Anal. Calcd for $C_{29}H_{26}FN_3O_4S$: C, 65.52; H, 4.93; N, 7.90. Found: C, 65.72; H, 4.68; N, 7.81.

***N*-(3-Ethoxypropyl)-4-(3-methoxybenzyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*19*}.** Yield: 64%. ^{1}H NMR (DMSO-d_6): δ 7.79 (t, J = 5.5 Hz, 1 H), 7.39−7.24 (m, 2 H), 7.17−7.04 (m, 2 H), 6.99 (t, J = 7.3 Hz, 1 H), 6.92 (d, J = 7.3 Hz, 1 H), 6.85 (d, J = 8.1 Hz, 1 H), 6.65 (t, J = 7.3 Hz, 1 H), 5.48 (s, 1 H), 5.05 (d, J = 16.2 Hz, 1 H), 4.66 (d, J = 13.8 Hz, 1 H), 4.38 (d, J = 16.2 Hz, 1 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 3.56 (d, J = 13.8 Hz, 1 H), 3.29−3.13 (m, 4 H), 3.14 (q, J = 6 Hz, 2 H), 1.60−1.48 (m, 2 H), 1.00 (t, J = 7 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 169.8, 169.6, 156.6, 136.3, 131.9, 128.0, 127.3, 127.0, 125.0, 121.0, 120.0, 119.4, 116.5, 110.2, 108.9, 104.6, 67.4, 65.2, 59.2, 55.1, 48.9, 36.9, 32.5, 29.9, 28.9, 14.9. HRMS: *m*/*z* 482.2106 (M^+). Anal. Calcd for $C_{25}H_{29}N_3O_4S$: C, 64.22; H, 6.25; N, 8.99. Found: C, 64.46; H, 6.12; N, 8.68.

4-[2-(2,4-Dimethoxyphenyl)ethyl]-*N*-(4-fluorobenzyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*21*}. Yield: 61%. ^{1}H NMR (DMSO-d_6): δ 8.30 (t, J = 6.2 Hz, 1 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.41 (d, J = 7.9 Hz, 1 H), 7.26−7.17 (m, 2 H), 7.17−6.99 (m, 4 H), 6.72 (d, J = 8,1 Hz, 1 H), 6.28 (d, J = 2.1 Hz, 1 H), 6.19 (dd, J = 8.1, 2.1 Hz, 1 H), 5.50(s, 1 H), 4.35 − 4.13 (m, 2 H), 4.20 (d, J = 13.9 Hz, 1 H), 4.13−3.97−3.86 (m, 1 H), 3.66 (s, 3 H), 3.62 (s, 3 H), 3.61 (s, 3 H), 3.39 (d, J = 13.8 Hz,1 H), 3.39−3.25 (m, 1 H), 2.57−2.41 (m, 2 H). ^{13}C NMR (DMSO-d_6): δ 170.2, 168.1, 161.1, 158.9, 157.8, 135.6 (2C), 131.8, 130.0, 129.3, 129.2, 127.7, 120.8, 119.4, 118.3, 116.4, 115.0, 114.7, 108.8, 104.5, 104.0, 97.9, 58.7, 55.2, 54.9, 49.8, 42.2. 31.7, 29.8, 27.4, HRMS: *m*/*z* 548.2020 (M^+), Anal. Calcd for $C_{30}H_{30}FN_3O_4S$: C, 65.80; H, 5.52; N, 7.67. Found: C, 65.92; H, 5.64; N, 7.46.

4-(1,3-Benzodioxol-5-yl)-*N*-(3-ethoxypropyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*22*}. Yield: 64%. ^{1}H NMR (DMSO-d_6): δ 7.57 (t, J = 5.5 Hz, 1 H), 7.54 (d, J = 8.1 Hz, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.13 (t, J = 8.1 Hz, 1 H), 7.02 (t, J = 8.1 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 1 H), 6.77 (d, J = 1.8 Hz, 1 H), 6.59 (dd, J = 8.3, 1.8 Hz, 1 H), 6.02 (s, 2 H), 5.59 (s, 1 H), 4.50 (d, J = 13.9 Hz, 1 H), 3.68 (s, 3 H), 3.64 (d, J = 13.9 Hz, 1 H), 3.32−3.11 (m, 6 H), 1.61−1.52 (m, 2 H), 0.95 (t, J = 6.8 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 169.6, 168.9, 147.2, 145.8, 138.6, 136.4, 131.9, 127.4, 121.1 (2C), 119.7, 116.4, 109.0, 108.0, 107.9, 103.8, 101.4, 67.6, 65.2, 62.3, 37.3, 32.4, 29.9, 28.9, 14.8. HRMS: *m*/*z* 482.1752 (M^+). Anal. Calcd for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.73. Found: C, 62.06; H, 5.71; N, 8.84.

4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-10-methyl-*N*-(3-methylbutyl)-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*23*}. Yield: 68%. ^{1}H NMR (DMSO-d_6): δ 7.69 (t, J = 5.7 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H), 7.01 (t, J = 7.9 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.58 (dd, J = 2.4, 8.5 Hz, 1H), 5.55 (s,1H), 4.61 (d, J = 13.8 Hz, 1H), 4.22 (s, 4H), 3.68 (s, 3H), 3.62 (d, J = 13.8 Hz, 1H), 3.11 (q, J = 6,4 Hz, 2H), 1.49 (sept, J = 6.4 Hz, 1H), 1.28 (q, J = 7.2 Hz, 2H), 0.83 (t, J = 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6): δ 169.4, 168.9, 143.0, 142.2, 138.0, 136.3, 131.9, 127.3, 121.0, 119.6, 119.3, 116.9, 116.5, 115.4, 109.0, 104.0, 64.1, 64.0, 62.3, 37.8 (2C), 32.5, 29.9, 25.2, 22.3 (2C). HRMS: m/z 480.1943 (M^+). Anal. Calcd for $C_{26}H_{29}N_3O_4S$: C, 65.11; H, 6.09; N, 8.76. Found: C, 65.29; H, 6.27; N, 8.53. Crystallographic data: monoclinic single crystal (0.35 × 0.20 × 0.12 mm^3, space group $P21/n$, unit cell constants a = 12.1930(14) Å, b = 12.6276(16) Å, c = 15.837(2) Å, α = 90°, β = 99.091(3)°, γ = 90°, V = 2407.8(5) Å^3, Z = 4, D_x = 1.323 Mg/m^3). The final R indices are R1 = 0.0912, wR2 = 0.1108.

***N*-Benzyl-10-methyl-4-(4-methyl-2-oxo-2*H*-chromen-7-yl)-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*24*}.** Yield: 73%. ^{1}H NMR (DMSO-d_6): δ 8.20 (t, J = 6.0 Hz, 1 H), 7.74 (d, J = 8.5 Hz, 1 H), 7.66 (d, J = 7.9 Hz, 1 H), 7.46 (d, J = 7.9 Hz 1 H), 7.37−7.08 (m, 8 H), 7.03 (t, J = 7.9 Hz, 1 H), 6.38 (s, 1 H), 5.97 (s, 1 H), 4.47−4.18 (m, 2 H), 4.40 (d, J = 13.9 Hz, 1 H), 3.70 (d, J = 13.9 Hz, 1 H), 3.68 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ 169.8, 168.6, 159.6, 153.0, 152.8, 146.8, 139.0, 136.5, 131.8, 128.2 (2C), 127.6, 127.1 (2C), 126.8, 125.6, 122.7, 121.1, 119.7, 118.0, 116.6, 114.2, 114.0, 109.1, 103.6, 61.4, 43.1, 32.2, 30.0, 18.0. HRMS: m/z 524.1644 (M^+). Anal. Calcd for $C_{30}H_{25}N_3O_4S$: C, 68.82; H, 4.81; N, 8.02. Found: C, 68.62; H, 4.58; N, 8.29.

***N*-Benzyl-4-(4-chloro-2-methoxy-5-methylphenyl)-10-methyl-3-oxo-3,4,5,10-tetrahydro-2*H*-[1,4]thiazepino[7,6-*b*]indole-5-carboxamide 6{*25*}.** Yield: 69%. ^{1}H NMR (DMSO-d_6): δ 8.81−8.15 (br s, 1 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.42 (d, J = 7.9 Hz, 1 H), 7.36−7.18 (m, 5 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.00 (t, J = 7.9 Hz, 1 H), 6.84 (br s, 1 H), 5.55 (s, 1 H), 5.45−4.62 (br m, 1 H), 4.47−4.09 (br m, 2 H), 3.69 (s, 3 H), 3.58 (d, J = 13.8 Hz, 1 H), 2.19 (br s, 3 H). ^{13}C NMR (DMSO-d_6): δ 170.0, 169.4, 153.2, 138.8, 136.2, 132.0, 131.9, 131.0, 128.2 (2C), 127.4 (3C), 126.9 (2C); 121.0, 119.3, 117.0, 116.9, 113.4, 108.8, 104.7, 61.5, 56.1, 43.0, 32.7, 29.9, 18.5. HRMS: m/z 520.1450 (M^+). Anal. Calcd for $C_{28}H_{26}ClN_3O_3S$: C, 64.67; H, 5.04; N, 8.08. Found: C, 64.41; H, 5.26; N, 8.31.

Ethyl *N*-{[4-(4-Methoxybenzyl)-10-methyl-3-oxo-2,3,4,5-tetrahydro[1,4]thiazepino[7,6-*b*]quinolin-5-yl]carbonyl}glycinate 7. A solution of aldehyde acid **3b** (104 mg, 0.4 mmol) and 4-methoxybenzylamine (55 mg, 0.4 mmol) in 3 mL of MeOH/DMSO/THF mixture (1:1:1) was kept for 1 h at rt. The reaction mixture was cooled to 0 °C, ethyl isocyanoacetate was added, and the solution was heated at 60 °C for 24 h. The solvent was evaporated in vacuo, and the resulting residue was purified by chromatography on silica gel, eluting with a gradient of 0−10% MeOH in CH_2Cl_2. Yield: 68%.^{1}H NMR (DMSO-d_6): δ 8.22 (t, J = 5.9 Hz, 1 H), 7.89 (s, 1 H), 7.53−7.56 (m, 2 H), 7.36 (t, J = 7.3 Hz, 1 H), 7.12−7.14 (m, 2 H), 6.60−6.62 (m, 2 H), 5.57 (s, 1 H), 5.13 (d, J = 14.6 Hz, 1 H), 4.52 (d, J = 15.0, 1 H), 4.26 (d, J = 14.6 Hz, 1 H), 4.10 (q, J = 6.9 Hz, 2 H), 3.88 (dd, J = 17.2, 5.9 Hz, 1 H), 3.75 (dd, J = 17.2, 5.9 Hz, 1 H), 3.50 (s, 3 H), 3.33 (d, J = 15.0 Hz, 1 H), 2.58 (s, 3 H), 1.18 (t, J = 6.9 Hz, 3 H). ^{13}C NMR (DMSO-d_6): δ 169.8, 169.7, 169.3, 158.5, 157.0, 145.6, 140.6, 134.4, 130.7, 129.5 (2C), 129.4, 125.9, 125.8, 125.5, 125.2, 113.6 (2C), 65.4, 60.9, 55.0, 51.7, 41.8, 31.8, 17.5, 14.2. HRMS: m/z 494.1744 (M^+).

General Procedure for Preparation of 1-Phenyl-3-methyl-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*f*][1,4]thiazepine-4-carboxamides 8a,b. The title compounds were prepared by condensation of **3c** with the corresponding amine and isocyanide using the same procedure, which was described for compounds **6**{*1*−*45*}. Compounds **8a**,**b** were purified by chromatography on silica gel, eluting with CH_2Cl_2.

***N*-Cycloheptyl-5-cyclohexyl-3-methyl-6-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*f*][1,4]thiazepine-4-carboxamide 8a.** Yield: 62%. ^{1}H NMR (DMSO-d_6): δ 7.65 (d, J = 8.5 Hz, 1 H), 7.56−7.36 (m, 5 H), 4.88 (s, 1 H), 4.37 (t, J = 10.0 Hz, 1 H), 4.10 (d, J = 13.8 Hz, 1 H), 3.77−3.61 (m, 1 H), 3.42 (d, J = 13.8 Hz, 1 H), 2.28 (s, 3 H), 1.86−1.02 (m, 22 H). ^{13}C NMR (DMSO-d_6): δ 168.0 (2C), 148.6, 138.6, 133.5, 129.3 (2C), 127.8, 123.6 (2C), 113.2, 54.2, 52.4, 50.9, 33.9, 33.8, 32.9, 30.2, 29.1, 27.4, 27.4 (2C), 25.4, 24.7, 24.0 (2C), 12.3. HRMS: m/z 481.2637 (M^+). Anal. Calcd for $C_{27}H_{36}N_4O_2S$: C, 67.47; H, 7.55; N, 11.66. Found: C, 67.19; H, 7.38; N, 11.51. Crystallographic data: monoclinic single crystal (0.40 × 0.15 × 0.05 mm^3), space group $P21/n$, unit cell constants a = 12.252(4) Å, b = 13.211(4) Å, c 17.676(5) Å, α = 90°, β = 102.16(2)°, γ = 90°, V = 2796.9(15) Å^3, Z = 4, D_x = 1.189 Mg/m^3. The final R indices are R1 = 0.0467, wR2 = 0.0835.

5-Benzyl-*N*-cycloheptyl-3-methyl-6-oxo-1-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*f*][1,4]thiazepine-4-carboxamide 8b. Yield: 65%. ^{1}H NMR (DMSO-d_6): δ 7.91 (d, J = 8.1 Hz, 1 H), 7.58−7.38 (m, 5 H), 7.32−7.15 (m, 5 H), 5.14 (d, J = 15.1 Hz, 1 H), 5.02 (s, 1 H), 4.52 (d, J = 13.8 Hz, 1 H), 4.38 (d, J = 15.1 Hz, 1 H), 3.75−3.68 (m, 1 H), 3.47 (d, J = 13.8 Hz, 1 H), 1.98 (s, 3 H), 1.81−1.24 (m, 12 H). ^{13}C NMR (DMSO-d_6): δ 168.8, 167.4, 136.3, 129.0, 124.7, 122.3, 119.2, 117.6, 110.2, 103.1, 54.2, 52.8, 51.1, 33.8 (2C), 33.8 (2C), 32.9, 30.5 (2C), 30.4, 29.0, 27.3 (2C), 25.3, 24.5, 24.0 (2C). HRMS: m/z 489.2317 (M^+). Anal. Calcd for $C_{28}H_{32}N_4O_2S$: C, 68.82; H, 6.60; N, 11.47. Found: C, 69.07; H, 6.88; N, 11.71.

General Procedure for Preparation of 6-Methyl-3-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-5-carboxamides 9a−d. The title compounds were prepared by condensation of **3d** with the corresponding amine and isocyanide using the same procedure, which was described for compounds **6**{*1*−*45*}, except the reaction mixture after addition of isocyanide was heated at reflux for 18 h. Compounds **9a**−**d** were purified by chromatography on silica gel, eluting with CH_2Cl_2. The title compounds were obtained as colorless solids in 56−70% yield.

***N*-Cycloheptyl-6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-5-carboxamide 9a.** Yield: 70%. ^{1}H NMR (DMSO-d_6): δ 7.97 (d, J = 7.9 Hz, 1 H), 7.77−7.57 (m, 3 H), 7.576−7.34 (m, 3 H), 7.26 (t, J = 7.9 Hz, 1 H), 7.11 (t, J = 7.9 Hz, 1 H), 5.76 (s, 1 H), 4.31 (d, J = 13.8 Hz, 1 H), 3.88−3.76 (m, 1 H), 3.66 (s, 3 H), 3.59 (d, J = 13.8 Hz, 1 H), 1.94−1.17 (m, 12 H). ^{13}C NMR (DMSO-d_6): δ 170.0, 166.6, 144.7, 136.6, 130.9, 130.4, 129.5, 127.6, 127.5, 125.0, 124.1, 123.7, 122.6, 122.0, 119.4, 117.9, 110.4, 104.3, 61.5, 51.3, 33.9, 33.8, 30.2, 27.3 (2C), 24.0 (2C). HRMS: m/z 516.2527 (M^+). Anal. Calcd for $C_{27}H_{28}F_3N_3O_2S$: C, 62.90; H, 5.47; N, 8.15. Found: C, 63.03; H, 5.69; N, 8.37.

***N*-Cycloheptyl-4-cyclohexyl-6-methyl-3-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-5-carboxamide 9b.** Yield: 76%. ^{1}H NMR (DMSO-d_6): δ 7.58 (d, J = 8.3 Hz, 1 H), 7.49 (d, J = 7.9 Hz, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.21 (t, J = 7.9 Hz, 1 H), 7.05 (t, J = 7.9 Hz, 1 H), 5.21 (s, 1 H), 4.41 (t, J = 11.1 Hz, 1 H), 3.86 (d, J = 13.8 Hz, 1 H), 3.80 (s, 3 H), 3.60−3.51 (m, 1 H), 3.40 (d, 13.8 Hz, 1 H), 2.00−0.90 (m, 22 H). ^{13}C NMR (DMSO-d_6): δ 168.8, 167.4, 136.3, 129.0, 124.7, 122.3, 119.2, 117.6, 110.2, 103.1, 54.2, 52.8, 51.1, 33.8 (2C), 32.9, 30.5 (2C), 30.4, 29.0, 27.3 (2C), 25.3, 24.5, 24.0 (2C). HRMS: m/z 454.2516 (M^+). Anal. Calcd for $C_{26}H_{35}N_3O_2S$: C, 68.84; H, 7.78; N, 9.26. Found: C, 69.04; H, 8.02; N, 9.04.

***N*-Benzyl-4-(4-methoxyphenyl)-6-methyl-3-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-5-carboxamide 9c.** Yield: 64%. ^{1}H NMR (DMSO-d_6): δ 8.54 (t, J = 6,0 Hz, 1 H), 7.50 (d, J = 8.1 Hz, 1 H),k 7.39 (d, J = 8.1 Hz, 1 H), 7.36−7.04 (m, 7 H), 7.17 (d, J = 9.0 Hz, 2 H), 6.92 (d, J = 9.0 Hz, 2 H), 5.68 (s, 1 H), 4.45 − 4.28 (m, 2 H), 4.03 (d, J = 13.8 Hz, 1 H), 3.74 (s, 3 H), 3.65 (s, 3 H), 3.46 (d, J = 13.8 Hz, 1 H). ^{13}C NMR (DMSO-d_6):

δ 169.3, 168.4, 157.8, 139.2, 137.4, 136.6, 128.2 (2C), 127.8 (2C), 127.3 (2C), 126.8, 124.9 (2C), 122.6, 119.4, 117.8, 114.1 (2C), 110.5, 103.7, 62.0, 55.3, 43.3, 33.0, 30.1. HRMS: *m*/*z* 472.1688 (M^+). Anal. Calcd for $C_{27}H_{25}N_3O_3S$: C, 68.77; H, 5.34; N, 8.91. Found: C, 68.64; H, 5.15; N, 8.69.

***N*-Benzyl-6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-5-carboxamide 9d.** Yield: 56%. ^{1}H NMR (DMSO-d_6): δ 8.59 (t, *J* = 5.7 Hz, 1 H), 7.75 (s, 1 H), 7.71−7.57 (m, 2 H), 7.57−7.18 (m, 9 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 5.95 (s, 1 H), 4.47−4.29 (m, 2 H), 4.02 (d, *J* = 14.0 Hz, 1 H), 3.70 (s, 3zH), 3.55 (d, *J* = 14.0 Hz, 1 H). HRMS: *m*/*z* 510.1460 (M^+). Anal. Calcd for $C_{27}H_{22}F_3N_3O_2S$: C, 63.64; H, 4.35; N, 8.25. Found: C, 63.91; H, 4.63; N, 8.51.

3-(2-Oxopropylsulfanyl)-1*H*-indole-2-carboxylic Acid 11. A solution of 3-mercapto-1*H*-indole-2-carboxylic acid **10** (19.3 g, 0.1 mol) in 200 mL of 10% aqueous Na_2CO_3 was treated with bromoacetone (16.4 g, 0.12 mol) at rt under stirring. The mixture was stirred at rt for 1 h and then acidified with diluted aqueous HCl until pH 3 was reached. The formed precipitate was filtered off, washed thoroughly with water, and dried to yield **11** (20 g, 80% yield), which was used at the next step without any further purification. ^{1}H NMR (DMSO-d_6): δ 11.49 (s, 1 H), 10.22 (br s 1 H), 7.45−7.26 (m, 4 H), 3.45 (s, 2 H), 1.8 (s, 3 H). HRMS: *m*/*z* 249.2932 (M^+). Anal. Calcd for $C_{26}H_{27}N_3O_5S$: C, 63.27; H, 5.51; N, 8.51. Found: C, 62.99; H, 5.22; N, 8.28.

General Procedure for Preparation of *N*-Cyclopentyl-3-methyl-5-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-3-carboxamides 12a−e. Equimolar amounts (0.5 mmol) of compound **11**, cyclopentyl isocyanide, and the corresponding benzylamine were dissolved in methanol (3 mL). The reaction mixture was stirred at rt for 2−3 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). On completion, the reaction mixture was cooled to rt, the formed precipitate was filtered off, and purified by chromatography on silica gel, eluting with a gradient of 0−10% MeOH in CH_2Cl_2.

4-(1,3-Benzodioxol-5-ylmethyl)-*N*-cyclopentyl-3-methyl-5-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-3-carboxamide 12a. Yield: 68%. ^{1}H NMR (DMSO-d_6): δ 11.57 (s, 1 H), 7.53−7.30 (m, 3 H), 7.21 (t, *J* = 7.9 Hz, 1 H), 7.10−6.98 (m, 2 H), 6.91−6.77 (m, 2 H), 5.97 (d, *J* = 3.4 Hz, 2 H), 5.00 (d, *J* = 16.2 Hz, 1 H), 4.44 (d, *J* = 16.2 Hz, 1 H), 3.92 (d, *J* = 13.8 Hz, 1 H), 3.63−3.55 (m, 1 H), 3.33 (d, *J* = 13.8 Hz, 1 H), 1.65−1.08 (m, 7 H), 1,51 (s, 3 H), 0.92−0.73 (m, 1 H). ^{13}C NMR (DMSO-d_6): δ 170.3, 164.5, 147.1, 145.6, 135.9, 133.5, 130.7, 126.1, 124.2, 119.5, 119.4, 112.2 (2C), 108.7, 107.8, 107.5, 100.7, 68.0, 51.0, 48.1, 42.5, 31.5, 31.4, 25.6, 23.5, 23.4. HRMS: *m*/*z* 478.1793 (M^+).

4-(4-Chlorobenzyl)-*N*-cyclopentyl-3-methyl-5-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-3-carboxamide 12b. Yield: 64%. ^{1}H NMR (DMSO-d_6): δ 11.56 (s, 1 H), 7.56−7.28 (m, 7 H),7.22 (t, *J* = 7.7 Hz, 1 H), 7.05 (t, *J* = 7.7 Hz, 1 H), 5.02 (d, *J* = 16.8 Hz, 1 H), 4.49 (d, *J* = 16.8 Hz, 1 H), 3.91 (d, *J* = 13.8 Hz, 1 H), 3.68−3.58 (m, 1 H), 3.39 (d, *J* = 13.8 Hz, 1 H), 1.69−1.09 Hz, 7 H), 1.51 (s, 3 H), 0.97−0.78 (m, 1 H). ^{13}C NMR (DMSO-d_6): δ 170.2, 164.2, 138.7, 135.8, 130.8, 130.3, 128.4 (2C), 127.9 (2C), 126.0, 124.4, 119.5, 119.4, 112.3 (2C), 109.4, 68.3, 51.0, 48.4, 42.4, 31.5, 31.4, 25.4, 23.5, 23.4. HRMS: *m*/*z* 478.1507 (M^+).

***N*-Cyclopentyl-3-methyl-4-(4-methylbenzyl)-5-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-3-carboxamide 12c.** Yield: 75%. ^{1}H NMR (DMSO-d_6): δ 11.47 (s, 1 H), 7.56−7.30 (m, 5 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.17−7.00 (m, 3 H), 5.05 (d, *J* = 16.0 Hz, 1 H), 4.47 (d, *J* = 16.0 Hz, 1ZH), 3.90 (d, *J* = 13.8 Hz, 1 H), 3.69−3.59 (m, *J* = (1 H), 3.35 (d, *J* = 13.8 Hz, 1 H), 2.26 (s, 3 H), 1.67−1.13 (m, 7 H), 1.51 (s, 3 H), 0.92−0.75 (m, 1 H); ^{13}C NMR (DMSO-d_6): δ 170.3, 164.2, 136.5, 135.8, 135.3, 130.6, 128.6 (2C), 126.5, 126.1, 124.3, 119.5, 119.4, 112.2 (2C), 109.1, 68.2, 51.0, 48.4, 42.6, 31.5, 31.4, 25.5, 23.5, 23.4, 20.6. HRMS: *m*/*z* 448.2056 (M^+).

***N*-Cyclopentyl-4-(4-fluorobenzyl)-3-methyl-5-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-3-carboxamide 12d.** Yield: 58%. ^{1}H NMR (DMSO-d_6): δ 11.47 (s, 1 H), 7.50−7.3 (m, 5 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.17−6.95 (m, 5 H), 5.07 (d, *J* = 16.0 Hz,1 H), 4.49 (d, *J* = 16.0 Hz, 1 H), 3.90 (d, *J* = 13.8 Hz, 1 H), 3.69 (q, *J* = 6.0 Hz, 1 H), 3.34 (d, *J* − 13.8 Hz, 1 H), 1.72−1.14 (m, 7 H), 1.53 (s, 3 H), 1.02−0.83 (m, 1 H). ^{13}C NMR (DMSO-d_6): δ 170.3, 164.3, 160.8, 135.8 (2C), 130.5, 128.5, 128.4, 126.0, 124.3, 119.5, 119.4, 114.8, 114.5, 112.3 (2C), 109.2, 68.2, 51.0, 48.2, 42.4, 31.5, 31.4, 25.5, 23.5, 12.4. HRMS: *m*/*z* 452.1800 (M^+).

4-Benzyl-*N*-cyclopentyl-3-methyl-5-oxo-3,4,5,6-tetrahydro-2*H*-[1,4]thiazepino[6,7-*b*]indole-3-carboxamide 12e. Yield: 63%. ^{1}H NMR (DMSO-d_6): δ 11.54 (s, 1 H), 7.5−7.0 (m, 10), 5.13 (d, *J* = 16.8 Hz, 1 H), 4.46 (d, *J* = 16.8 Hz, 1 H), 3.90 (d, *J* = 13.8 Hz, 1 H), 3.70 (q, *J* = 6.2 Hz, 1 H), 3.33 (d, *J* = 13.8 Hz, 1 H), 1.52 (s, 3 H), 1.67−0.8 (m, 8 H). ^{13}C NMR (DMSO-d_6): δ 170.3, 164.2, 139.6, 135.8, 130.5, 128.0 (2C), 126.5 (2C), 125.3, 126.1, 124.3, 119.5, 119.4, 112.3, 109.2, 68.3, 51.0, 48.8, 42.6, 31.5, 31.4, 25.5, 23.5, 23.4. HRMS: *m*/*z* 434.1904 (M^+).

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Supporting Information Available: Structures and yields of compounds **6**{*26*−*45*} and spectral and crystallographic data for the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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