Solution-Phase Parallel Synthesis of Diverse 1,5-Benzodiazepin-2-ones

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A practical and efficient parallel method has been developed for the synthesis of 1,5-benzodiazepin-2-ones with a large variety of substituents at the 3-, 4-, 5-, 7-, and 8-positions using 1,5-difluoro-2,4-dinitrobenzene as the starting material. All the reactions involved here are highly effective in giving the desired products under mild conditions.

Introduction

Benzodiazepines are the prototypical privileged substructure. It was this class of compounds to which the term "privileged structure" was first applied by Evans et al.[1] The therapeutic applications of benzodiazepines include anxiolytics,[2] antiarrhythmics,[3] vasopressin antagonists,[4] HIV reverse transcriptase inhibitors,[5] and cholecystokinin antagonists.[6] Molecules with the 1,5-benzodiazepin-2-one scaffold are privileged substructures exhibiting a range of biological activities. Some of them have been clinically used as anxiolytic agents, such as arfendazam **1**,[7] lofendazam **2**,[8] triflubazam **3**,[9] and clobazam **4**,[10] or as antisecretory agents, such as telenzepine **5**.[11] Furthermore, they exhibit activities including interleukin-1β converting enzyme inhibition, such as for **6**, delayed rectifier potassium current blocking, such as for **7**,[12] and antiarrhythmic activity, such as for **8**[13] (Figure 1). Significantly less research has been undertaken on the 1,5-benzodiazepin-2-ones, compared to the 1,4-benzodiazepin-2-ones. Therefore, development of a synthetic method that could be used to prepare a variety of these templates remains an important task.

Recently, our group reported the synthesis of 2-hydroxyquinoxaline,[14] benzimidazole,[15] imidazoquinoxalinol,[16] indolin-2-one,[17] benzo[1,4]oxazin-3- one,[18] benzo[1,4]thiazin-3-one,[19] and 1,5-benzothiazepin-4-one[20] libraries using 1,5-difluoro-2,4-dinitrobenzene (DFDNB) as starting material. Herein, we wish to report a novel and efficient solution-phase route to synthesis of substituted 1,5-benzodiazepin-2-ones. This route permits us to introduce great molecular diversity under mild reaction conditions, including substitution diversity and scaffold diversity. A large number of derivatives can be rapidly synthesized in excellent purity and high yield using this method.

Results and Discussion

The synthetic route to 5,7,8-substituted 1,5-benzodiazepin-2-ones is depicted in Scheme 1. The quantitative substitution of the first fluorine atoms of DFDNB by ethanethiol, phenols, or secondary amines produced compound **2**. Displacement of another fluorine atom with β-amino esters **3** gave **4**. Sulfone is an interesting pharmacophore displayed on many drugs. Therefore, we attempted to oxidize **4** to its corresponding sulfone, **5,** where R^1 is the sulfide group. UHP[19] (an adduct of hydrogen peroxide and urea) has been optimized in our group to prepare aromatic sulfones from the sulfide treatment of compound **4** with UHP, and readily provided **5**. The convenient reductive method of $HCOONH_4$ with Pd/C was then chosen for quantitative reduction of *m*-Ar$(NO_2)_2$ of **4** or **5** into *m*-Ar$(NH_2)_2$ at room temperature that offered compound **6** in high purity. Additional alkali hydrolysis (LiOH) of **6** was necessary to give the desired acid **7**. Cyclization of **7** with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) smoothly afforded the benzodiazepine derivative **8**. Compound **8** was further treated using aldehydes, anhydride, isocyanates, isothiocyanate, and sulfonyl chlorides to generate the corresponding secondary amines, amides, ureas, thioureas, and sulfonamides, respectively. Typical compounds were characterized by LC-MS, HRMS (Table 1), ^{1}H, or ^{13}CNMR.

Because not many substituted β-amino esters were commercially available, we decided to employ a simple route to prepare a variety of β-amino esters.[21] The requisite β-amino esters **3** were prepared as shown in Scheme 1. Various primary amines were selectively condensed with 1 equiv methyl acrylate to give **3**. The product reacted with **2** directly without further purification.

To obtain the 1,5-benzodiazepin-2-one core with more points of diversity, we selected some substituted β-amino acids **9** as nucleophilic reagents (Scheme 2). The resulting intermediate **2a** was used to undergo S_NAr-type reactions, in which the fluorine can be substituted by the β-amino group of **9**. Compound **10** was oxidized by UHP to obtain the corresponding sulfone **11**. Compounds **10** and **11** were reduced using stannous chloride in the presence of hydrochloric acid (38%), and spontaneously cyclized to afford the desired benzodiazepine-2-one scaffolds **12** and **13**. There are two amino groups (5- and 8-amino) in structures **12** and **13**, and we had to derive them respectively. It was soon realized, however, that the 8-amino group is more prone to reaction than the 5-amino of **12**. Therefore, **12** was treated with isocyanates to generate the corresponding ureas **14**. However, the 8-amino group of **13** is less prone to reaction because of the electron-withdrawing effect

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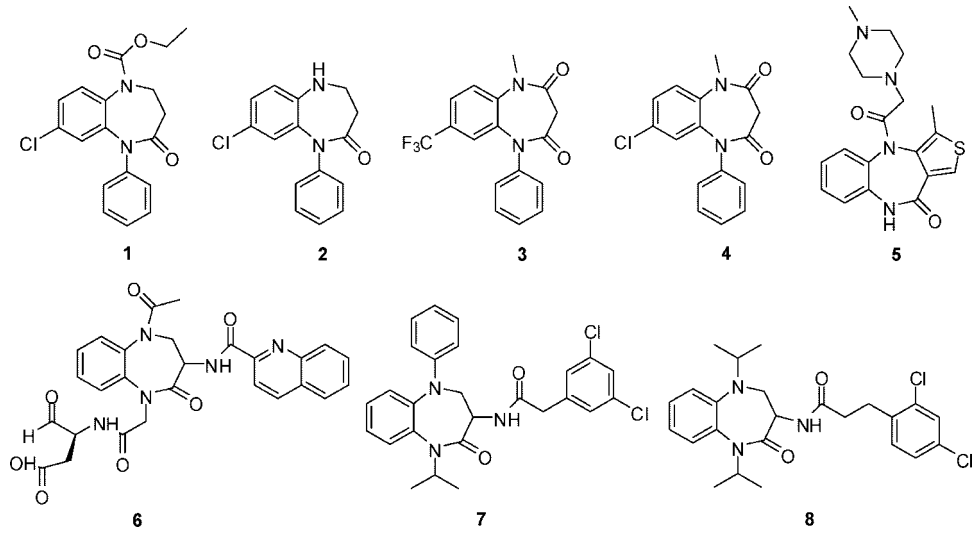
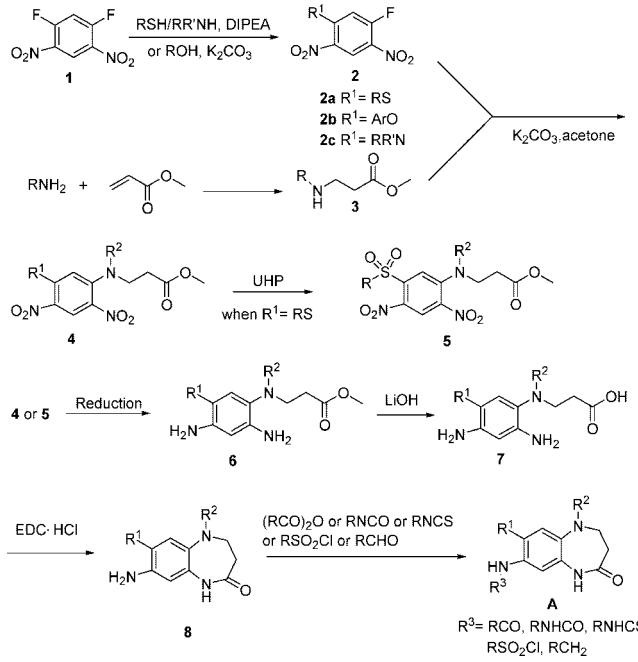


Figure 1. Examples of some biologically active 1,5-benzodiazepin-2-ones.

Scheme 1. Synthetic Route to 5,7,8-Substituted 1,5-Benzodiazepin-2-ones



of the ortho–sulfone group. Therefore, when compounds **13** were treated with isocyanates, the corresponding ureas **15** were generated. The remaining steps completing the synthetic sequence involved further functionalization of the free amino group of the 1,5-benzodiazepin-2-one template. We initially attempted the derivation of the 5-amino group of **14** and 8-amino group of **15** with anhydrides or isocyanates, but we observed that the amino group is too inert to react with isocyanates. Finally, **14** was treated with substituent benzyl chloride or anhydride to obtain **16**. Compound **15** was treated with substituent benzyl chloride or anhydride and we obtained **17** and **18**. Typical compounds were characterized by LC-MS, HRMS (Table 2), ^{1}H, or ^{13}CNMR.

Conclusions

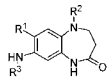
In conclusion, we have created a versatile, high-yielding, solution-phase route to substituted 1,5-benzodiazepin-2-ones from DFDNB. All the reactions involved herein are highly effective under mild conditions. The biological screening results from this library for the identification of active compounds will be reported soon.

Experimental Section

All chemical reagents were purchased from Acros Organics (Geel, Belgium) and used without further purification. Tetrahydrofuran (THF) was dried over molecular sieves and redistilled from sodium before use. Acetone was treated with anhydrous K_2CO_3. HPLC analysis or purification was performed on a Gilson HPLC system equipped with a Gilson UV–vis-152 detector, a Gilson 322 pump, and a Gilson 215 liquid handler. The employed column was a Kromasil C18 column (4.6 μm, 4.6 mm $\times$ 50 mm) from DIKMA for analysis. The eluent was a mixture of acetonitrile and water containing 0.05% HCOOH with a linear gradient from 5:95 (v:v) acetonitrile-H_2O to 95:5 (v:v) acetonitrile-H_2O within five minutes at 1 mL/min. UV absorption detection was conducted at 254 nm. Automatic LC-MS analysis was performed on a ThermoFinnigan LCQ-Advantage mass spectrometer equipped with an Agilent pump, an Agilent detector, an Agilent liquid handler, and a fluent splitter. The elution gradient, flow rate, and detection wavelength were the same as indicated above. Five percent of the eluent was split into the MS system. Mass spectra were recorded in either the positive or the negative ion mode using electrospray ionization (ESI). High resolution LC-MS was carried out by Agilent LC/MSD TOF using a column of Agilent ZORBAX SB-C18 (Rapid resolution, 3.5 μm, 2.1 mm $\times$ 30 mm) at a flow rate of 0.40 mL/min. The solvent was MeOH: water = 75:25 (v:v) containing 5 mmol/L ammonium formate. The ion source was also ESI. All NMR experiments were carried out on a Varian Mercury 300 or 400 MHz NMR spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. Parallel synthesis was carried out on an H + P Labortechnik parallel synthesizer.

General Procedure for the Synthesis of Intermediate 2. Method 1. To a magnetically stirred solution of 1.0 equiv. (typically 5.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene and 1.0 equiv. of *N*-diisopropylethylamine (DIPEA) in 50 mL

Table 1. Molecular Weight and HPLC Purity for the Representative Substituted 1,5-Benzodiazepin-2-ones **A**



Entry	R^1	R^2	R^3	HPLC purity[a] (%)	HRMS (M + H$^+$) found	HRMS (M + H$^+$) calcd.
A1			H	99.0	402.2180	402.2182
A2				99.3	444.2291	444.2287
A3				99.9	498.2020	498.2005
A4				100.0	539.2484	539.2458
A5				99.5	542.2116	542.2114
A6				99.1	438.2766	438.2790
A7			H	99.0	340.1696	340.1695
A8				99.5	396.2328	396.2321
A9			H	99.0	374.1540	374.1538
A10				100.0	430.2157	430.2164
A11				97.6	424.2643	424.2634
A12				99.2	458.2484	458.2477
A13				100.0	382.1806	382.1801
A14				99.0	436.1529	436.1518
A15				99.2	527.1954	527.1940
A16				100.0	489.2180	489.2172
A17				99.1	505.1956	505.1943
A18				98.0	477.1979	477.1972
A19				98.9	493.1743	493.1743
A20				99.0	480.1624	480.1627

Entry	R^1	R^2	R^3	HPLC purity[a] (%)	HRMS (M + H$^+$) found	HRMS (M + H$^+$) calcd.
A21				97.7	492.2337	492.2321
A22				99.9	416.1618	416.1644
A23				99.0	470.1362	470.1361
A24				98.5	561.1796	561.1783
A25				100.0	523.2033	523.2015
A26				100.0	539.1789	539.1787
A27				99.2	511.1819	511.1815
A28				99.5	527.1586	527.1587
A29				99.1	514.1479	514.1470
A30			H	98.8	303.2192	303.2185
A31			H	100.0	312.1385	312.1382
A32				99.2	354.1494	354.1488
A33				99.7	408.1218	408.1205
A34				100.0	499.1648	499.1627
A35				99.4	461.1872	461.1859
A36				99.1	477.1624	477.1630
A37				100.0	449.1660	449.1659
A38				99.9	465.1447	465.1430
A39				99.0	452.1331	452.1314

[a] Purity based on the integration area of the HPLC peaks (the detection wavelength was 254 nm).

of THF was added dropwise a solution of 1.0 equiv of ethanethiol or amine in 25 mL of THF. The reaction mixture was continuously stirred for an additional 1 h at room temperature. After the solvent was evaporated, water was added to precipitate **2**. The desired intermediate **2a** and **2c** then were collected by filtration and washed thoroughly with water. Intermediate **2** was not purified and was used directly for the next reaction. For a typical compound, ethyl(5-fluoro-2,4-dinitrophenyl)sulfane, 1.21 g of yellow powder, was obtained in 98% yield, with an HPLC purity >99%. ESI-MS: m/z 245.1 $(M-H)^-$.

Method 2. To a magnetically stirred solution of 1.0 equiv (typically 5.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene in 20 mL of acetone, 1.0 equiv of phenol and 2.0 equiv. of anhydrous K_2CO_3 were added. The reaction mixture was shaken mechanically at room temperature for more than 5 h until the total disappearance of **1** as monitored by HPLC. Undissolved excess K_2CO_3 was removed by filtration. The solvent was evaporated. The residue **2b** was used directly for the next reaction. Typical compound, 1-(3,5-dimethylphenoxy)-5- fluoro-2,4-dinitrobenzene, 1.49 g of yellow powder, was obtained in 98% yield, with an HPLC purity >99%. ESI-MS: m/z 305.1 $(M-H)^-$.

General Procedure for the Synthesis of Intermediate 4. A three-necked, 250 mL round-bottomed flask provided with a pressure-equalizing dropping funnel, thermometer, and CaCl drying tube was charged with MeOH (50 mL) and primary amine (6.0 mmol). The mixture was stirred magnetically and then cooled to 0–5 °C (ice-bath), while methyl acrylate (6.6 mmol) in 40 mL MeOH was added dropwise over 1 h. The mixture was stirred at room temperature for 48 h and concentrated under vacuum. The residue **3** was dissolved in 50 mL THF and added to the intermediate **2** (5.0 mmol). The reaction mixture was continuously stirred for 4 h at room temperature. The reaction mixture was evaporated in vacuo to dryness. Water (30 mL) was added to precipitate **4** as a yellow solid. Then compound **4** was collected after thoroughly washing with water. For a typical compound, methyl 3-((5-(3,5-dimethylphenoxy)-2,4-dinitrophenyl)(phenethyl)amino)propanoate 2.34 g of yellow pow-

Scheme 2. Synthetic Route to 1,5-Benzodiazepin-2-ones with More Substituted Groups

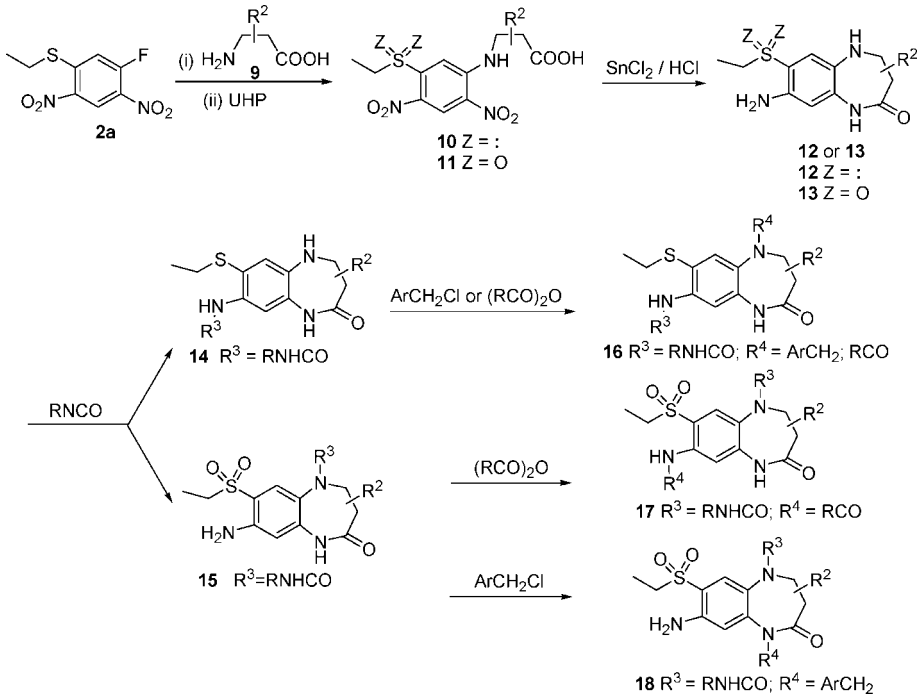
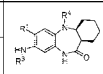
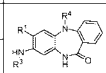
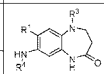
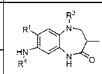
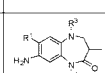


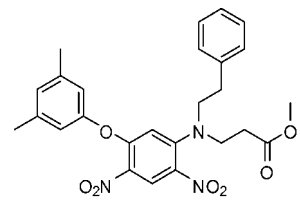
Table 2. Molecular Weight and HPLC Purity for the Representative Substituted 1,5-Benzodiazepin-2-ones

Entry	Core structure	R^1	R^3	R^4	HPLC purity[a] (%)	HRMS (M + H$^+$) found	HRMS (M + H$^+$) calcd.
12a			H	H	100.0	292.1490	292.1481
14a			H	H	99.2	429.1765	429.1760
16a					100.0	525.1563	525.1583
16b					100.0	553.1829	553.1840
16c					100.0	537.2145	537.2136
12b			H	H	98.9	286.1021	286.1014
14b			H	H	99.2	423.1299	423.1291
16d					100.0	547.1128	547.1171
13a			H	H	99.5	270.0901	270.0912
15a			H	H	100.0	407.1192	407.1189
13b			H	H	99.6	284.1059	284.1069
15b			H	H	100.0	421.1351	421.1346
17a					100.0	517.1182	517.1169
18					100.0	545.1428	545.1426

[a] Purity based on the integration area of the HPLC peaks (the detection wavelength was 254 nm).

der was obtained in 95% yield, with an HPLC purity >99%. ESI-MS: m/z 494.2 $(M+H)^+$.

Methyl 3-((5-(3,5-dimethylphenoxy)-2,4-dinitrophenyl)(phenethyl)amino) propanoate. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.269 (s, 6H), 2.552 (t, 2H, J = 6.9 Hz), 2.691 (t, 2H, J = 7.2 Hz), 3.293 (t, 2H, J = 7.2 Hz), 3.393 (t, 2H, J = 6.9 Hz), 3.522 (s, 3H), 6.432 (s, 1H), 6.815 (s, 2H), 6.947–6.991 (m, 3H), 7.186 (s, 1H), 7.192–7.215 (m, 2H), 8.590 (s, 1H).



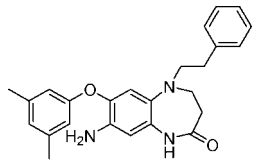
typical compound of **4**

General Procedure for the Synthesis of Intermediate 5. To a solution of **4** (3 mmol) in acetonitrile (15 mL) at 0 °C, UHP (18 mmol) and trifluoroacetic anhydride (10 mmol) in 30 mL acetonitrile were slowly added with stirring. The oxidative progress was then monitored by a fast LC-MS analysis. After the completion of oxidation, the mixture was diluted with water (30 mL), and extracted with DCM (3 × 30 mL). The DCM layers were combined and washed with a saturated NaCl solution (1 × 30 mL), and dried over anhydrous $MgSO_4$. The solid was then filtered and the filtrate was concentrated in vacuo to obtain solid of **5**. The solid was used directly for the next reaction without further purification. For a typical compound, methyl 3-((5-(ethylsulfonyl)-2,4-dinitrophenyl)(phenethyl)amino)propanoate 1.36 g of yellow powder was obtained in 98% yield, with an HPLC purity >99%. ESI-MS: m/z 466.1 $(M+H)^+$.

General Procedure for the Synthesis of Intermediate 8. To a stirred solution of 3.0 mmol of **4** or **5** in 50 mL of ethanol was added $HCOONH_4$ (30 mmol) and 0.2 g of 10% Pd/C. The reaction mixture turned from yellow to red and finally became colorless within 30 min at room temperature. The catalyst and excess $HCOONH_4$ were removed by filtration. The filtrate was concentrated in vacuo to yield **6**.

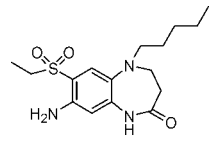
2.0 mmol **6** was dissolved in 20 mL of THF; 1.05 g of $LiOH•H_2O$ in 20 mL water was added with stirring. The reaction mixture was continuously stirred for 1 h at room temperature. The pH was adjusted to 7.0 with 2 N HCl. The resulting solution was analyzed by LC-MS at 254 nm and showed a single peak with the anticipated molecular weight, for example 3-((2,4-diamino-5-(ethylsulfonyl)phenyl) (phenethyl)amino)propanoic acid with m/z 392.2 $(M+H)^+$. This solution was directly added to EDC•HCl (6 mmol) and allowed to react for an additional 3 h until completion as monitored by a fast LC-MS system. The mixture was concentrated in vacuo to remove THF and extracted with EtOAc (3 × 50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether. For a typical compound, 8-amino-7-(ethylsulfonyl)-5-phenethyl-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one 520 mg of pale powder was obtained in 70% yield, with an HPLC purity >99%. ESI-MS: m/z 374.1 $(M+H)^+$.

8-Amino-7-(3,5-dimethyl-phenoxy)-5-phenethyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.173 (s, 6H), 2.237 (t, 2H, J = 6.6 Hz), 2.605 (t, 2H, J = 7.2 Hz), 3.017 (t, 2H, J = 7.2 Hz), 3.297 (t, 2H, J = 6.6 Hz), 4.762 (brs, 2H), 6.449 (s, 1H), 6.537 (s, 2H), 6.561 (s, 1H), 6.674 (s, 1H), 7.001–7.022 (m, 2H), 7.131–7.208 (m, 3H), 9.279 (s, 1H).



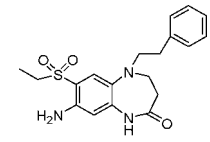
compound **A1**

8-Amino-7-ethanesulfonyl-5-pentyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.840 (t, 3H, J = 6.9 Hz), 1.256–1.305 (m, 7H), 1.496–1.505 (m, 2H), 2.515 (t, 2H, J = 6.6 Hz), 3.062 (t, 2H, J = 7.2 Hz), 3.190 (q, 2H, J = 6.9 Hz), 3.447 (t, 2H, J = 6.6 Hz), 4.995 (brs, 2H), 6.446 (s, 1H), 7.418 (s, 1H), 8.120 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 7.093, 13.868, 21.832, 26.516, 28.637, 33.885, 47.663, 52.179, 55.535, 109.226, 113.650, 121.157, 131.013, 141.556, 143.378, 172.895.



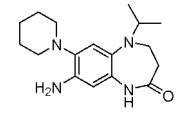
compound **A7**

8-Amino-7-ethanesulfonyl-5-phenethyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ1.098 (t, 3H, J = 7.2 Hz), 2.299 (t, 2H, J = 6.9 Hz), 2.683 (t, 2H, J = 7.2 Hz), 3.148 (t, 2H, J = 7.2 Hz), 3.177 (q, 2H, J = 7.2 Hz), 3.356 (t, 2H, J = 6.9 Hz), 5.916 (brs, 2H), 6.479 (s, 1H), 7.165–7.258 (m, 6H), 9.703 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 7.139, 33.336, 33.901, 47.724, 54.345, 55.596, 109.348, 113.773, 121.203, 126.039, 128.267, 128.603, 130.754, 139.679, 141.556, 143.555, 172.834.



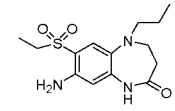
compound **A9**

8-Amino-5-isopropyl-7-piperidin-1-yl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.095 (d, 6H, J = 6.3 Hz), 1.450–1.505 (m, 2H), 1.509–1.543 (m, 4H), 2.184 (t, 2H, J = 6.9 Hz), 2.612–2.788 (m, 4H), 3.286–3.311 (m, 1H), 3.391 (t, 2H, J = 6.9 Hz), 4.535 (brs, 2H), 6.263 (s, 1H), 6.648 (s, 1H), 9.064 (s, 1H).



compound **A30**

8-Amino-7-ethanesulfonyl-5-propyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.795 (t, 3H, J = 7.6 Hz), 1.090 (t, 3H, J = 7.6 Hz), 1.386–1.440 (m, 2H), 2.279 (t, 2H, J = 6.8 Hz), 2.897 (t, 2H, J = 6.8 Hz), 3.165 (q, 2H, J = 7.6 Hz), 3.231 (t, 2H, J = 6.8 Hz), 5.787 (brs, 2H), 6.459 (s, 1H), 7.086 (s, 1H), 9.668 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 7.048, 11.320, 20.154, 33.916, 47.739, 54.071, 55.322, 109.241, 113.773, 121.142, 131.212, 141.541, 143.433, 172.925.

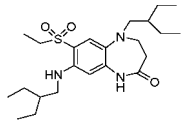


compound **A31**

Derivation of 8 at 8-aromatic amino group. Method 1. Aldehydes (0.1 mmol), $NaBH(OAc)_3$ (0.2 mmol), and glacetic acid (100 μL) were added to a solution of **8** (0.1 mmol) in 5 mL anhydrous DCM. The reaction mixture was stirred mechanically on an H + P Labortechnik parallel synthesizer at 45 °C for at least 12 h. The chemical conversion was monitored by LC-MS analysis. After the reaction was complete, the solution was evaporated in vacuo to dryness. The crude residue was dissolved again with 15 mL DCM and then was washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL). After it had completely dried over anhydrous Na_2SO_4, the filtrate was concentrated in vacuo to obtain the crude product. The final products were characterized after chromatographic purification on silica gel. The yields ranged from 70 to 90%.

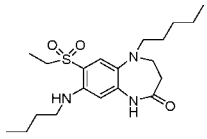
7-Ethanesulfonyl-5-(2-ethyl-butyl)-8-(2-ethyl-butylamino)-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.796 (t, 6H, J = 7.5 Hz), 0.924 (t, 6H, J = 7.5 Hz), 1.227 (t, 3H, J = 7.2 Hz), 1.252–1.318 (m, 4H), 1.340–1.427 (m, 4H), 1.452–1.589 (m, 2H), 2.482 (t, 2H, J = 6.9 Hz), 2.884 (d, 2H, J = 7.2 Hz), 2.984 (t, 2H,

J = 4.5 Hz), 3.138 (q, 2H, J = 7.2 Hz), 3.391 (t, 2H, J = 6.9 Hz), 5.943 (brs, 1H), 6.325 (s, 1H), 7.423 (s, 1H), 7.800 (s, 1H).



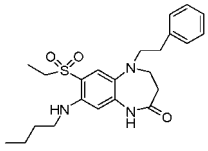
compound **A6**

8-Butylamino-7-ethanesulfonyl-5-pentyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.848 (t, 3H, J = 6.9 Hz), 0.947 (t, 3H, J = 7.5 Hz), 1.240–1.289 (m, 7H), 1.356–1.482 (m, 4H), 1.605–1.703 (m, 2H), 2.518 (t, 2H, J = 6.9 Hz), 3.046–3.109 (m, 4H), 3.150 (q, 2H, J = 7.5 Hz), 3.462 (t, 2H, J = 6.9 Hz), 6.002 (brs, 1H), 6.334 (s, 1H), 7.513 (s, 1H), 7.611 (s, 1H).



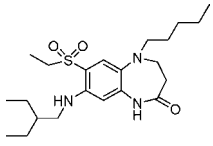
compound **A8**

8-Butylamino-7-ethanesulfonyl-5-phenethyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.976 (t, 3H, J = 7.2 Hz), 1.278 (t, 3H, J = 7.2 Hz), 1.414–1.488 (m, 2H), 1.613–1.688 (m, 2H), 2.531 (t, 2H, J = 6.9 Hz), 2.798 (t, 2H, J = 7.5 Hz), 3.095 (t, 2H, J = 6.9 Hz), 3.155 (q, 2H, J = 7.2 Hz), 3.341 (t, 2H, J = 7.5 Hz), 3.532 (t, 2H, J = 6.9 Hz), 6.348 (s, 1H), 7.139–7.294 (m, 5H), 7.582 (s, 1H), 7.605 (s, 1H).



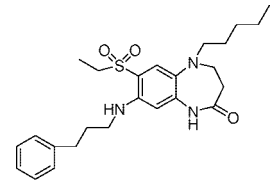
compound **A10**

7-Ethanesulfonyl-8-(2-ethyl-butylamino)-5-pentyl-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.785 (t, 3H, J = 6.9 Hz), 0.843 (t, 6H, J = 7.5 Hz), 1.074 (t, 3H, J = 7.2 Hz), 1.161–1.215 (m, 4H), 1.296–1.410 (m, 6H), 1.511–1.553 (m, 1H), 2.302 (t, 2H, J = 6.9 Hz), 2.919–2.988 (m, 4H), 3.175 (q, 2H, J = 7.2 Hz), 3.226 (t, 2H, J = 6.9 Hz), 5.902 (brs, 1H), 6.416 (s, 1H), 7.168 (s, 1H), 9.672 (s, 1H).



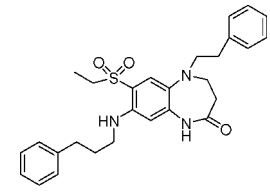
compound **A11**

7-Ethanesulfonyl-5-pentyl-8-(3-phenyl-propylamino)-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.807 (t, 3H, J = 6.9 Hz), 1.089 (t, 3H, J = 7.2 Hz), 1.148–1.221 (m, 4H), 1.346–1.412 (m, 2H), 1.853–1.902 (m, 2H), 2.302 (t, 2H, J = 6.9 Hz), 2.656 (t, 2H, J = 7.2Hz), 2.945 (t, 2H, J = 6.9 Hz), 3.066–3.085 (m, 2H), 3.191 (q, 2H, J = 7.2 Hz), 3.265 (t, 2H, J = 6.9 Hz), 5.926 (brs, 1H), 6.401 (s, 1H), 7.180–7.305 (m, 6H), 9.640 (s, 1H).



compound **A12**

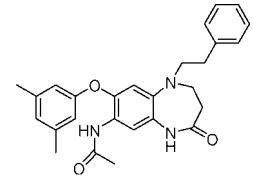
7-Ethanesulfonyl-5-phenethyl-8-(3-phenyl-propylamino)-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.108 (t, 3H, J = 7.2 Hz), 1.858–1.907 (m, 2H), 2.328 (t, 2H, J = 6.6 Hz), 2.633–2.716 (m, 4H), 3.075–3.093 (m, 2H), 3.182 (t, 2H, J = 6.6 Hz), 3.231 (q, 2H, J = 7.2 Hz), 3.364 (t, 2H, J = 6.6 Hz), 5.940 (brs, 1H), 6.424 (s, 1H), 7.149–7.306 (m, 11H), 9.667 (s, 1H).



compound **A21**

Method 2. To a solution of 0.10 mmol of **8** in 5 mL of anhydrous DCM, 0.12 mmol of different acylating reagents (anhydride, isocyanate, or isothiocyanate) were added. The reaction mixture was stirred mechanically on an H + P Labortechnik parallel synthesizer at 45 °C for at least 4 h. The solvent then was evaporated in vacuo to obtain the crude product. The final products were characterized after chromatographic purification on silica gel. The yields ranged from 70 to 90%.

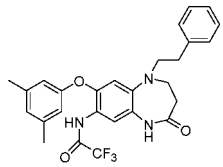
***N*-[8-(3,5-Dimethyl-phenoxy)-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl]-acetamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.992 (s, 3H), 2.193 (s, 6H), 2.294 (t, 2H, J = 6.6 Hz), 2.588 (t, 2H, J = 7.2 Hz), 3.048 (t, 2H, J = 7.2 Hz), 3.424 (t, 2H, J = 6.6 Hz), 6.566 (s, 1H), 6.628 (s, 2H), 6.768 (s, 1H), 6.940–6.965 (m, 2H), 7.142–7.209 (m, 3H), 7.566 (s, 1H), 9.348 (s, 1H), 9.430 (s, 1H).



compound **A2**

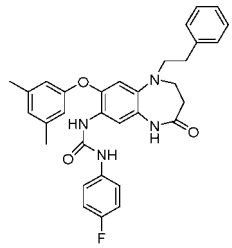
***N*-[8-(3,5-Dimethyl-phenoxy)-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl]-2,2,2-trifluoro-**

acetamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.191 (s, 6H), 2.357 (t, 2H, J = 6.6 Hz), 2.637 (t, 2H, J = 7.2 Hz), 3.130 (t, 2H, J = 7.2 Hz), 3.475 (t, 2H, J = 6.6 Hz), 6.618 (s, 2H), 6.631 (s, 1H), 6.779 (s, 1H), 6.967–6.984 (m, 2H), 7.008 (s, 1H), 7.154–7.215 (m, 3H), 9.495 (s, 1H), 10.852 (s, 1H).



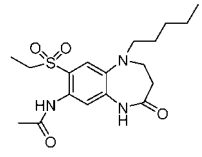
compound **A3**

1-[8-(3,5-Dimethyl-phenoxy)-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl]-3-(4-fluoro-phenyl)-urea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.210 (s, 6H), 2.289 (t, 2H, J = 6.8 Hz), 2.589 (t, 2H, J = 7.6 Hz), 3.039 (t, 2H, J = 7.6 Hz), 3.383 (t, 2H, J = 6.8 Hz), 6.595 (s, 1H), 6.672 (s, 2H), 6.789 (s, 1H), 6.946–6.966 (m, 2H), 7.079–7.7.201 (m, 5H), 7.401–7.435 (m, 2H), 7.908 (s, 1H), 8.264 (s, 1H), 9.207 (s, 1H), 9.439 (s, 1H).



compound **A4**

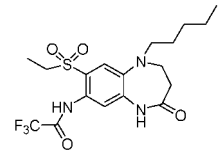
***N*-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-acetamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.819 (t, 3H, J = 6.9 Hz), 1.090 (t, 3H, J = 7.2 Hz), 1.200–1.249 (m, 4H), 1.432–1.476 (m, 2H), 2.066 (s, 3H), 2.381 (t, 2H, J = 6.9 Hz), 3.074 (t, 2H, J = 7.2 Hz), 3.290 (q, 2H, J = 7.2 Hz), 3.418 (t, 2H, J = 6.9 Hz), 7.354 (s, 1H), 7.499 (s, 1H), 9.382 (s, 1H), 9.893 (s, 1H).



compound **A13**

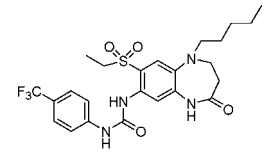
***N*-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-2,2,2-trifluoro-acetamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.830 (t, 3H, J = 6.9 Hz), 1.098 (t, 3H, J = 7.2 Hz), 1.229–1.246 (m, 4H), 1.432–1.507 (m, 2H), 2.448 (t, 2H, J = 6.9 Hz), 3.143 (t, 2H, J = 6.9 Hz), 3.318 (q, 2H, J = 7.2 Hz), 3.477 (t, 2H, J = 6.9 Hz), 7.287 (s, 1H), 7.407 (s, 1H), 9.966 (s, 1H), 10.954 (s, 1H).

1-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-trifluoromethyl-phenyl)-urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.823 (t, 3H, J = 6.9 Hz), 1.128 (t, 3H, J = 7.2 Hz), 1.230–1.254 (m, 4H),



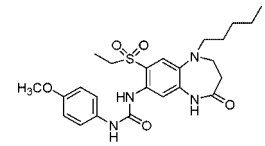
compound **A14**

1.401–1.454 (m, 2H), 2.376 (t, 2H, J = 6.6 Hz), 3.062 (t, 2H, J = 6,9 Hz), 3.294 (q, 2H, J = 7.2 Hz), 3.404 (t, 2H, J = 6.6 Hz), 7.347 (s, 1H), 7.623–7.699 (m, 5H), 8.516 (s, 1H), 9.891 (s, 1H), 10.147 (s, 1H).



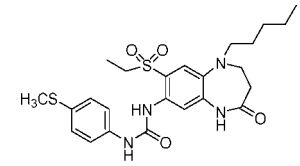
compound **A15**

1-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-methoxy-phenyl)-urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.820 (t, 3H, J = 6.9 Hz), 1.124 (t, 3H, J = 7.2 Hz), 1.230–1.254 (m, 4H), 1.401–1.450 (m, 2H), 2.359 (t, 2H, J = 6.6 Hz), 3.044 (t, 2H, J = 6,9 Hz), 3.270 (q, 2H, J = 7.2 Hz), 3.326 (t, 2H, J = 6.6 Hz), 3.683 (s, 3H), 6.870 (d, 2H, J = 9.0 Hz), 7.340 (d, 2H, J = 9.0 Hz), 7.387 (s, 1H), 7.715 (s, 1H), 8.343 (s, 1H), 9.562 (s, 1H), 9.862 (s, 1H).



compound **A16**

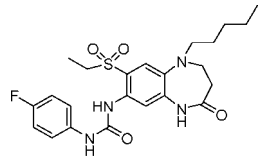
1-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-methylsulfanyl-phenyl)-urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.823 (t, 3H, J = 6.9 Hz), 1.126 (t, 3H, J = 7.2 Hz), 1.229–1.252 (m, 4H), 1.399–1.491 (m, 2H), 2.389 (t, 2H, J = 6.6 Hz), 2.426 (s, 3H), 3.053 (t, 2H, J = 6,9 Hz), 3.314 (q, 2H, J = 7.5 Hz), 3.394 (t, 2H, J = 6.6 Hz), 7.218 (d, 2H, J = 8.7 Hz), 7.334 (s, 1H), 7.440 (d, 2H, J = 8.7 Hz), 7.694 (s, 1H), 8.402 (s, 1H), 9.762 (s, 1H), 9.869 (s, 1H).



compound **A17**

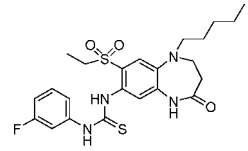
1-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-fluoro-phenyl)-urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.823 (t, 3H, J = 6.9 Hz), 1.126 (t, 3H, J = 7.2 Hz), 1.204–1.253 (m, 4H), 1.428–1.471 (m, 2H), 2.367 (t, 2H, J = 6.6 Hz), 3.054 (t, 2H, J = 6,9 Hz), 3.297 (q, 2H, J = 7.2 Hz), 3.394 (t, 2H, J

= 6.6 Hz), 7.094–7.153 (m, 2H), 7.334 (s, 1H), 7.455–7.502 (m, 2H), 7.690 (s, 1H), 8.398 (s, 1H), 9.779 (s, 1H), 9.873 (s, 1H).



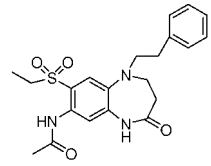
compound **A18**

1-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(3-fluoro-phenyl)-thiourea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.837 (t, 3H, J = 6.9 Hz), 1.094 (t, 3H, J = 7.2 Hz), 1.200–1.310 (m, 4H), 1.455–1.505 (m, 2H), 2.426 (t, 2H, J = 6.6 Hz), 3.097 (t, 2H, J = 6,9 Hz), 3.246 (q, 2H, J = 7.2 Hz), 3.454 (t, 2H, J = 6.6 Hz), 6.872–7.035 (m, 1H), 7.183 (s, 1H), 7.262–7.289 (m, 1H), 7.368 (s, 1H), 7.370–7.396 (m, 1H), 7.668–7.704 (m, 1H), 9.248 (s, 1H), 9.906 (s, 1H), 10.434 (s, 1H).



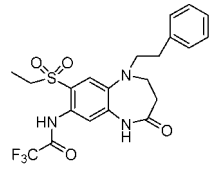
compound **A19**

***N*-(8-Ethanesulfonyl-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-acetamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.103 (t, 3H, J = 7.2 Hz), 2.069 (s, 3H), 2.401 (t, 2H, J = 6.9 Hz), 2.757 (t, 2H, J = 7.2 Hz), 3.266 (t, 2H, J = 7.2 Hz), 3.290 (q, 2H, J = 7.2 Hz), 3.511 (t, 2H, J = 6.9 Hz), 7.187–7.297 (m, 5H), 7.436 (s, 1H), 7.500 (s, 1H), 9.395 (s, 1H), 9.921 (s, 1H).



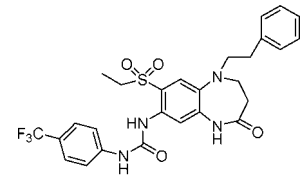
compound **A22**

***N*-(8-Ethanesulfonyl-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-2,2,2-trifluoro-acetamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.110 (t, 3H, J = 7.2 Hz), 2.462 (t, 2H, J = 6.6 Hz), 2.797 (t, 2H, J = 6.9 Hz), 3.324 (q, 2H, J = 7.2 Hz), 3.399 (t, 2H, J = 6.9 Hz), 3.559 (t, 2H, J = 6.6 Hz), 7.191–7.296 (m, 6H), 7.480(s, 1H), 9.977 (s, 1H), 10.966 (s, 1H).



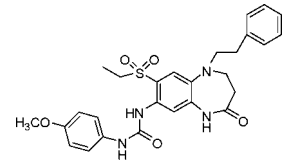
compound **A23**

1-(8-(ethylsulfonyl)-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-(trifluoromethyl)phenyl)urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.145 (t, 3H, J = 7.2 Hz), 2.400 (t, 2H, J = 6.9 Hz), 2.758(t, 2H, J = 7.6 Hz), 3.280 (q, 2H, J = 7.2 Hz), 3.334 (t, 2H, J = 7.6 Hz), 3.502 (t, 2H, J = 6.9 Hz), 7.187–7.277 (m, 5H), 7.431 (s, 1H), 7.624–7.672 (m, 4H), 7.694(s, 1H), 8.521 (s, 1H), 9.910 (s, 1H), 10.152 (s, 1H).



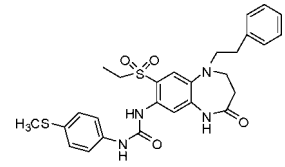
compound **A24**

1-(8-(ethylsulfonyl)-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-methoxyphenyl)urea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.143 (t, 3H, J = 7.2 Hz), 2.386 (t, 2H, J = 6.9 Hz), 2.751(t, 2H, J = 7.6 Hz), 3.288 (q, 2H, J = 7.2 Hz), 3.314 (t, 2H, J = 7.6 Hz), 3.486 (t, 2H, J = 6.9 Hz), 3.706 (s, 3H), 6.869 (d, 2H, J = 8.8 Hz), 7.186–7.363 (m, 5H), 7.385 (d, 2H, J = 8.8 Hz), 7.412 (s, 1H), 7.731 (s, 1H), 8.348 (s, 1H), 9.562 (s, 1H), 9.876 (s, 1H).



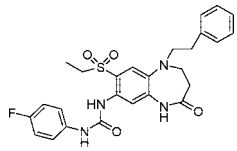
compound **A25**

1-(8-(Ethylsulfonyl)-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-(methylthio)phenyl)urea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.143 (t, 3H, J = 7.6 Hz), 2.392 (t, 2H, J = 6.9 Hz), 2.427 (s, 3H), 2.755(t, 2H, J = 7.6 Hz), 3.297 (q, 2H, J = 7.6 Hz), 3.314 (t, 2H, J = 7.6 Hz), 3.492 (t, 2H, J = 6.9 Hz), 7.187–7.291 (m, 7H), 7.425 (d, 2H, J = 8.8 Hz), 7.452 (s, 1H), 7.709 (s, 1H), 8.407 (s, 1H), 9.761 (s, 1H), 9.883 (s, 1H).



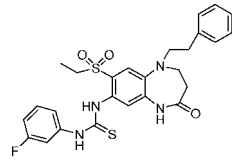
compound **A26**

1-(8-Ethanesulfonyl-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-fluoro-phenyl)-urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.141 (t, 3H, J = 7.2 Hz), 2.390 (t, 2H, J = 6.9 Hz), 2.752(t, 2H, J = 6.9 Hz), 3.297 (q, 2H, J = 7.2 Hz), 3.492 (t, 2H, J = 7.2 Hz), 3.685 (t, 2H, J = 6.9 Hz), 7.097–7.127 (m, 2H), 7.157–7.300 (m, 5H), 7.418 (s, 1H), 7.458–7.504 (m, 2H), 7.703(s, 1H), 8.408 (s, 1H), 9.797 (s, 1H), 9.907 (s, 1H).



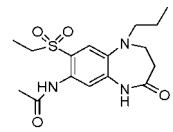
compound **A27**

1-(8-Ethanesulfonyl-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(3-fluoro-phenyl)-thiourea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.110 (t, 3H, J = 7.2 Hz), 2.443 (t, 2H, J = 6.6 Hz), 2.798(t, 2H, J = 6.6 Hz), 3.284 (q, 2H, J = 7.2 Hz), 3.388 (t, 2H, J = 6.6 Hz), 3.545 (t, 2H, J = 6.6 Hz), 6.985–7.011 (m, 1H), 7.172–7.311 (m, 6H), 7.348–7.424 (m, 1H), 7.445 (s, 1H), 7.664–7.717 (m, 1H), 7.941(s, 1H), 9.272 (s, 1H), 9.934 (s, 1H), 10.444 (s, 1H).



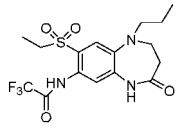
compound **A28**

***N*-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-acetamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.824 (t, 3H, J = 7.2 Hz), 1.100 (t, 3H, J = 7.2 Hz), 1.453–1.507 (m, 2H), 2.067 (s, 3H), 2.388 (t, 2H, J = 6.4 Hz), 3.047 (t, 2H, J = 6.8 Hz), 3.294 (q, 2H, J = 7.2 Hz), 3.414 (t, 2H, J = 6.4 Hz), 7.354 (s, 1H), 7.507 (s, 1H), 9.382 (s, 1H), 9.890 (s, 1H).



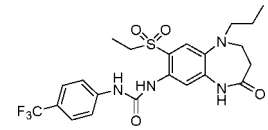
compound **A32**

***N*-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-2,2,2-trifluoro-acetamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.841 (t, 3H, J = 7.2 Hz), 1.107 (t, 3H, J = 7. Two Hz), 1.488–1.542 (m, 2H), 2.455 (t, 2H, J = 6.4 Hz), 3.116 (t, 2H, J = 7.2 Hz), 3.332 (q, 2H, J = 7.2 Hz), 3.473 (t, 2H, J = 6.4 Hz), 7.297 (s, 1H), 7.407 (s, 1H), 9.964(s, 1H), 10.951 (s, 1H).



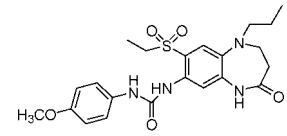
compound **A33**

1-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-trifluoromethyl-phenyl)-urea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.830 (t, 3H, J = 7.2 Hz), 1.138 (t, 3H, J = 7.2 Hz), 1.455–1.509 (m, 2H), 2.384 (t, 2H, J = 6.4 Hz), 3.038 (t, 2H, J = 7.2 Hz), 3.300 (q, 2H, J = 7.2 Hz), 3.403 (t, 2H, J = 6.4 Hz), 7.347 (s, 1H), 7.628–7.694 (m, 5H), 8.517 (s, 1H), 9.886 (s, 1H), 10.139 (s, 1H).



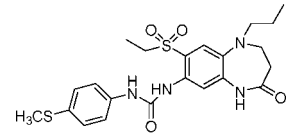
compound **A34**

1-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-methoxy-phenyl)-urea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.825 (t, 3H, J = 7.2 Hz), 1.134 (t, 3H, J = 7.2 Hz), 1.446–1.500 (m, 2H), 2.369 (t, 2H, J = 6.8 Hz), 3.020 (t, 2H, J = 7.2 Hz), 3.284 (q, 2H, J = 7.2 Hz), 3.385 (t, 2H, J = 6.8 Hz), 3.705 (s, 3H), 6.867 (d, 2H, J = 8.8 Hz), 7.327 (s, 1H), 7.372 (d, 2H, J = 8.8 Hz), 7.717 (s, 1H), 8.344 (s, 1H), 9.553 (s, 1H), 9.857 (s, 1H).



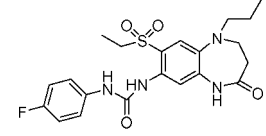
compound **A35**

1-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-methylsulfanyl-phenyl)-urea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.827 (t, 3H, J = 7.2 Hz), 1.135 (t, 3H, J = 7.2 Hz), 1.449–1.503 (m, 2H), 2.375 (t, 2H, J = 6.8 Hz), 2.427 (s, 3H), 3.027 (t, 2H, J = 7.2 Hz), 3.291 (q, 2H, J = 7.2 Hz), 3.391 (t, 2H, J = 6.8 Hz), 7.218 (d, 2H, J = 8.8 Hz), 7.334 (s, 1H), 7.439 (d, 2H, J = 8.8 Hz), 7.695 (s, 1H), 8.403 (s, 1H), 9.753 (s, 1H), 9.865 (s, 1H).



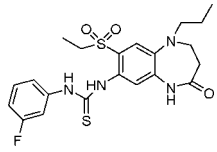
compound **A36**

1-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(4-fluoro-phenyl)-urea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.826 (t, 3H, J = 7.2 Hz), 1.135 (t, 3H, J = 7.2 Hz), 1.449–1.502 (m, 2H), 2.374 (t, 2H, J = 6.8 Hz), 3.027 (t, 2H, J = 7.2 Hz), 3.293 (q, 2H, J = 7.2 Hz), 3.391 (t, 2H, J = 6.8 Hz), 7.122 (t, 2H, J = 8.8 Hz), 7.334 (s, 1H), 7.461–7.496 (m, 2H), 7.692 (s, 1H), 8.400 (s, 1H), 9.771 (s, 1H), 9.869 (s, 1H).



compound **A37**

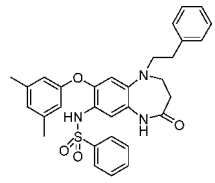
1-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-3-(3-fluoro-phenyl)-thiourea. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.853 (t, 3H, J = 7.2 Hz), 1.104 (t, 3H, J = 7.2 Hz), 1.496–1.550 (m, 2H), 2.433 (t, 2H, J = 6.4 Hz), 3.091 (t, 2H, J = 7.2 Hz), 3.282 (q, 2H, J = 7.2 Hz), 3.449 (t, 2H, J = 6.4 Hz), 6.987 (t, 1H, J = 8.0 Hz), 7.193 (s, 1H), 7.278 (d, 1H, J = 8.0 Hz), 7.367 (s, 1H), 7.392–7.412 (m, 1H), 7.685 (d, 1H, J = 11.2 Hz), 9.245 (s, 1H), 9.905 (s, 1H), 10.432 (s, 1H).



compound **A38**

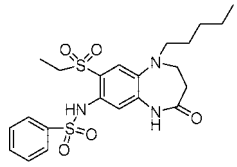
Method 3. To a solution of 0.10 mmol of **8** in 5 mL of dry DCM, 0.3 mmol of pyridine and 0.12 mmol of sulfonyl chloride were added. After the reaction mixture was stirred at 45 °C for more than 5 h, the solvent was evaporated in vacuo. The final products were characterized after chromatography purification on silica gel. The yields ranged from 70 to 90%.

***N*-[8-(3,5-Dimethyl-phenoxy)-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl]-benzenesulfonamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.131 (s, 6H), 2.284 (t, 2H, J = 6.4 Hz), 2.519 (t, 2H, J = 7.6 Hz), 2.979 (t, 2H, J = 7.6 Hz), 3.389 (t, 2H, J = 6.4 Hz), 6.196 (s, 2H), 6.329 (s, 1H), 6.723 (s, 1H), 6.866–6.885 (m, 2H), 7.012 (s, 1H), 7.128–7.181 (m, 3H), 7.457 (t, 2H, J = 7.6 Hz), 7.571 (t, 1H, J = 7.6 Hz), 7.711 (d, 2H, J = 7.6 Hz), 9.456 (s, 1H), 9.728 (s, 1H).



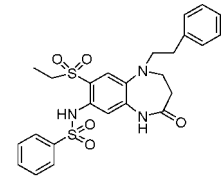
compound **A5**

***N*-(8-Ethanesulfonyl-4-oxo-1-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-benzenesulfonamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.797 (t, 3H, J = 7.2 Hz), 0.980 (t, 3H, J = 7.2 Hz), 1.163–1.206 (m, 4H), 1.389–1.433 (m, 2H), 2.358 (t, 2H, J = 6.6 Hz), 3.037 (t, 2H, J = 7.2 Hz), 3.166 (q, 2H, J = 7.2 Hz), 3.395 (t, 2H, J = 6.6 Hz), 6.995 (s, 1H), 7.288 (s, 1H), 7.580–7.693 (m, 3H), 7.901–7.929 (m, 2H), 9.442 (s, 1H), 9.973 (s, 1H).



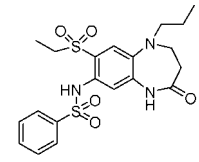
compound **A20**

***N*-(8-Ethanesulfonyl-4-oxo-1-phenethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-benzenesulfonamide.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.996 (t, 3H, J = 7.5 Hz), 2.398 (t, 2H, J = 6.9 Hz), 2.716(t, 2H, J = 7.5 Hz), 3.205 (q, 2H, J = 7.5 Hz), 3.216 (t, 2H, J = 7.5 Hz), 3.485 (t, 2H, J = 6.9 Hz), 7.001 (s, 1H), 7.151–7.278 (m, 5H), 7.368(s, 1H), 7.585–7.696 (m, 3H), 7.907–7.936 (m, 2H), 9.466 (s, 1H), 9.998 (s, 1H).



compound **A29**

***N*-(8-Ethanesulfonyl-4-oxo-1-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)-benzenesulfonamide.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.795 (t, 3H, J = 7.2 Hz), 0.993 (t, 3H, J = 7.2 Hz), 1.417–1.471 (m, 2H), 2.365 (t, 2H, J = 6.4 Hz), 3.008 (t, 2H, J = 6.8 Hz), 3.164 (q, 2H, J = 7.2 Hz), 3.389 (t, 2H, J = 6.4 Hz), 7.001 (s, 1H), 7.287 (s, 1H), 7.607 (t, 2H, J = 7.6 Hz), 7.693 (t, 1H, J = 7.6 Hz), 7.917 (d, 2H, J = 7.6 Hz), 9.436 (s, 1H), 9.973 (s, 1H).



compound **A39**

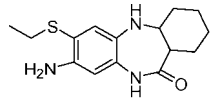
General Procedure for the Synthesis of Intermediate 10. To a magnetically stirred solution of 1.0 equiv (5.0 mmol) intermediate **2a** and 2.0 equiv of DIPEA in 50 mL THF was added 1.0 equiv of β-amine acid. The reaction mixture was continuously stirred for 4 h at room temperature. The reaction mixture was evaporated in vacuo to dryness. The residue **10** was used directly for the next reaction. For a typical compound, 2-(5-(ethylthio)-2,4-dinitrophenylamino)benzoic acid 1.724 g of yellow powder was obtained in 95% yield, with an HPLC purity >99%. ESI-MS: m/z 362.1 $(M-H)^-$.

General Procedure for the Synthesis of Intermediate 11. To a solution of **10** (3 mmol) in acetonitrile (30 mL) at 0 °C, UHP (18 mmol) and trifluoroacetic anhydride (10 mmol) in 30 mL acetonitrile were slowly added under stirring. The oxidative progress was then monitored by fast LC-MS analysis. After the completion of oxidation, the mixture was diluted with water (30 mL), and extracted with DCM (3 × 30 mL). The DCM layers were combined and washed with a saturated NaCl solution (1 × 30 mL) and dried over anhydrous $MgSO_4$. The solid then was filtered and the filtrate was concentrated in vacuo to obtain solid of **11**. The solid was used directly for the next reaction without further purification. For a typical compound, 2-(5-(ethylsulfonyl)-2,4-dinitrophenylamino)benzoic acid, 1.15 g of yellow

powder was obtained in 96% yield, with an HPLC purity >99%. ESI-MS: m/z 396.1 $(M+H)^+$.

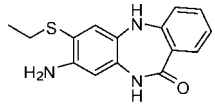
General Procedure for the Synthesis of 12 and 13. Compound **10** or **11** (3 mmol) in 30 mL of ethanol was completely reduced by adding it to a mixture of $SnCl_2 \cdot 2H_2O$ (18 mmol) and 12 M HCl (2 mL) under reflux for 4 h. The chemical conversion was monitored by LC-MS analysis. After the reaction was completed, the pH value must be carefully adjusted to 10. The resulting mixture was extracted with DCM (3 × 30 mL). The organic phase was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether. For a typical compound, 8-amino-7-(ethylsulfonyl)- 5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one 740 mg of pale powder was obtained in 78% yield, with an HPLC purity >96%. ESI-MS: m/z 318.1 $(M+H)^+$.

8-Amino-7-ethylsulfanyl-1,2,3,4,4a,5,10,11a-octahydrodibenzo[*b*,*e*][1,4]diazepin-11-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.773 (t, 3H, J = 7.2 Hz), 1.225–1.422 (m, 4H), 1.692–1.730 (m, 1H), 1.859–1.918 (m, 1H), 1.978–2.033 (m, 1H), 2.161–2.202 (m, 1H), 2.572 (q, 2H, J = 7.2 Hz), 2.620–2.758 (m, 2H), 5.154 (brs, 1H), 5.552 (brs, 2H), 6.298 (s, 1H), 6.562 (s, 1H), 8.475 (s, 1H).



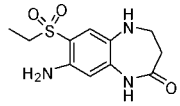
compound **12a**

8-Amino-7-(ethylthio)-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.105 (t, 3H, J = 7.2 Hz), 2.643 (q, 2H, J = 7.2 Hz), 5.011 (brs, 2H), 6.355 (s, 1H), 6.807–6.861 (m, 1H), 6.905 (d, 1H, J = 7.8 Hz), 6.960 (s, 1H), 7.252–7.308 (m, 1H), 7.414 (s, 1H), 7.605–7.636 (d, 1H, J = 7.8 Hz), 9.797 (s, 1H).



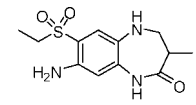
compound **12b**

8-Amino-7-(ethylsulfonyl)-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.085 (t, 3H, J = 7.2 Hz), 2.404 (t, 2H, J = 6.3 Hz), 3.126 (q, 2H, J = 7.2 Hz), 3.352 (t, 2H, J = 6.3 Hz), 5.133 (brs, 1H), 5.501 (brs, 2H), 6.426 (s, 1H), 7.097 (s, 1H), 8.706 (s, 1H).



compound **13a**

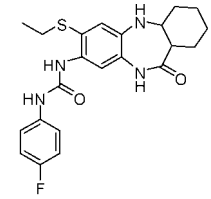
8-Amino-7-(ethylsulfonyl)-3-methyl-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.943 (d, 3H, J = 6.9 Hz), 1.085 (t, 3H, J = 7.2 Hz), 2.573–2.613 (m, 1H), 2.999–3.071 (m, 1H), 3.127 (q, 2H, J = 7.2 Hz), 3.365–3.400 (m, 1H), 5.050 (brs, 1H), 5.521 (brs, 2H), 6.418 (s, 1H), 7.104 (s, 1H), 9.699 (s, 1H).



compound **13b**

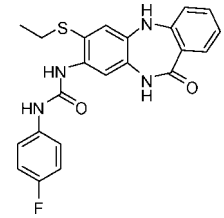
General Procedure for the Synthesis of 14 and 15. To a solution of 0.50 mmol of **12** or **13** in 10 mL of anhydrous DCM, 0.55 mmol of isocyanate was added. The reaction mixture was stirred mechanically on an H + P Labortechnik parallel synthesizer at room temperature for at least 12 h. The chemical conversion was monitored by LC-MS analysis. The solvent then was evaporated in vacuo to obtain the crude product. The final products **14** and **15** were characterized after chromatography purification on silica gel. The yields ranged from 70 to 90%.

1-(7-(Ethylthio)-11-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)-3-(4-fluorophenyl)urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.138 (t, 3H, J = 7.2 Hz), 1.187–1.224 (m, 2H), 1.320–1.495 (m, 2H), 1.620–1.660 (m, 1H), 1.709–1.748 (m, 1H), 1.832–1.977 (m, 2H), 2.661 (brs, 1H), 2.774 (q, 2H, J = 7.2 Hz), 2.889 (brs, 1H), 5.155 (brs, 1H), 7.074 (s, 1H), 7.103–7.133 (m, 2H), 7.423–7.470 (m, 2H), 7.563 (s, 1H), 8.035 (s, 1H), 9.402 (s, 1H), 9.472 (s, 1H).



compound **14a**

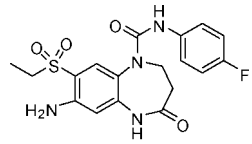
1-(7-(Ethylthio)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)-3-(4-fluorophenyl)urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.669 (t, 3H, J = 7.5 Hz), 2.270 (q, 2H, J = 7.5 Hz), 6.369–6.418 (m, 1H), 6.447–6.471 (m, 1H), 6.592–6.622 (m, 2H), 6.654 (s, 1H), 6.807–6.836 (m, 1H), 6.924–6.984 (m, 2H), 7.161–7.187 (m, 1H), 7.196 (s, 1H), 7.270 (s, 1H), 7.601 (s, 1H), 8.943 (s, 1H), 9.435 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.329, 28.675, 113.761, 115.220, 118.525, 118.853, 119.636, 120.669, 122.587, 124.277, 130.121, 132.139, 133.187, 134.900, 135.236, 136.117, 150.291, 152.381, 157.255, 167.768.



compound **14b**

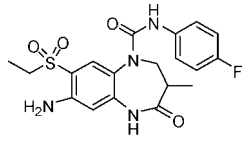
7-Amino-8-(ethylsulfonyl)-*N*-(4-fluorophenyl)-4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-1-carboxamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.084 (t, 3H, J =

7.2 Hz), 2.437 (t, 2H, J = 6.3 Hz), 3.126 (q, 2H, J = 7.2 Hz), 3.937 (t, 2H, J = 6.3 Hz), 6.207 (brs, 2H), 6.580 (s, 1H), 7.007–7.046 (m, 2H), 7.283 (s, 1H), 7.360–7.395 (m, 2H), 8.180 (s, 1H), 9.980 (s, 1H).



compound **15a**

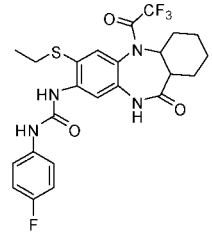
7-Amino-8-(ethylsulfonyl)-*N*-(4-fluorophenyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-1-carboxamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.968 (d, 3H, J = 6.6 Hz), 1.079 (t, 3H, J = 7.2 Hz), 2.645–2.688 (m, 1H), 3.152 (q, 2H, J = 7.2 Hz), 3.589–3.624 (m, 1H), 3.805–3.915 (m, 1H), 6.213 (brs, 2H), 6.573 (s, 1H), 6.997–7.057 (m, 2H), 7.285 (s, 1H), 7.394–7.346 (m, 2H), 8.160 (s, 1H), 9.986 (s, 1H).



compound **15b**

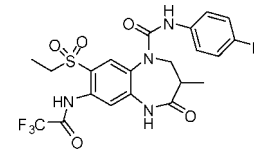
General Procedure for the Synthesis of 16, 17, and 18. Method 1. To a solution of 0.10 mmol of **14** or **15** in 5 mL of anhydrous DCM, 0.12 mmol of anhydride was added. The reaction mixture was stirred mechanically on an H + P Labortechnik parallel synthesizer at 45 °C for at least 12 h. The solvent then was evaporated in vacuo to obtain the crude product. The final products were characterized after chromatography purification on silica gel. The yields ranged from 70 to 90%.

1-(7-(Ethylthio)-11-oxo-5-(2,2,2-trifluoroacetyl)-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)-3-(4-fluorophenyl)urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.011 (t, 3H, J = 7.2 Hz), 1.034–1.163 (m, 4H), 2.754 (q, 2H, J = 7.2 Hz), 3.286–3.394 (m, 4H), 3.354–3.891 (m, 2H), 7.041–7.101 (m, 2H), 7.359–7.406 (m, 2H), 7.692 (s, 1H), 7.762 (s, 1H), 8.638 (s, 1H), 10.348 (s, 1H), 11.064 (s, 1H).



compound **16a**

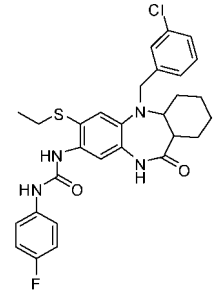
8-(Ethylsulfonyl)-*N*-(4-fluorophenyl)-3-methyl-4-oxo-7-(2,2,2-trifluoroacetamido)-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-1-carboxamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.033 (d, 3H, J = 6.9 Hz), 1.059 (t, 3H, J = 7.5 Hz), 2.706–2.789 (m, 1H), 3.394 (q, 2H, J = 7.2 Hz), 3.853–3.893 (m, 2H), 7.041–7.101 (m, 2H), 7.358–7.406 (m, 2H), 7.692 (s, 1H), 7.759 (s, 1H), 8.637 (s, 1H), 10.347 (s, 1H), 11.065 (s, 1H).



compound **17a**

Method 2. To a solution of **14** or **15** (0.1 mmol) in 5 mL anhydrous acetone was added benzyl chloride (0.15 mmol), K_2CO_3 (0.3 mmol), and KI (0.1 mmol). The reaction mixture was stirred mechanically on an H + P Labortechnik parallel synthesizer at 45 °C for at least 12 h. The chemical conversion was monitored by LC-MS analysis. After the reaction was complete, the solution was evaporated in vacuo to dryness. The crude residue was redissolved with 15 mL DCM and then washed with water (2 × 10 mL). The solvent then was evaporated in vacuo to obtain the crude product. The final products were characterized after chromatographic purification on silica gel. The yields ranged from 70 to 90%.

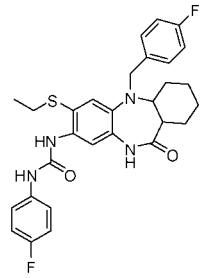
1-(5-(3-Chlorobenzyl)-7-(ethylthio)-11-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)-3-(4-fluorophenyl)urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.770 (t, 3H, J = 7.2 Hz), 1.222–1.414 (m, 4H), 1.699–1.739 (m, 1H), 1.854–1.896 (m, 1H), 2.003–2.105 (m, 1H), 2.183–2.219 (m, 1H), 2.586 (q, 2H, J = 7.2 Hz), 2.620–2.759 (m, 2H), 4.464 (s, 2H), 7.068–7.253 (m, 7H), 7.403–7.450 (m, 2H), 7.695 (s, 1H), 8.052 (s, 1H), 9.462 (s, 1H), 9.639 (s, 1H).



compound **16b**

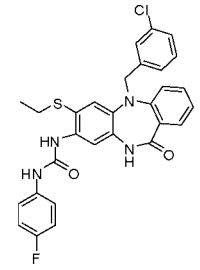
1-(7-(Ethylthio)-5-(4-fluorobenzyl)-11-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)-3-(4-fluorophenyl)urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.773 (t, 3H, J = 7.2 Hz), 1.227–1.423 (m, 4H), 1.694–1.731 (m, 1H), 1.858–1.908 (m, 1H), 1.988–2.030 (m, 1H), 2.165–2.203 (m, 1H), 2.582 (q, 2H, J = 7.2 Hz), 2.622–2.756 (m, 2H), 4.447 (s, 2H), 6.980–7.126 (m, 5H), 7.192–7.239 (m, 2H), 7.402–7.449 (m, 2H), 7.683 (s, 1H), 8.040 (s, 1H), 9.454 (s, 1H), 9.613 (s, 1H).

1-(5-(3-chlorobenzyl)-7-(ethylthio)-11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-8-yl)-3-(4-fluorophenyl)urea. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.146 (t, 3H, J = 7.5 Hz), 2.804 (q, 2H, J = 7.5 Hz), 5.203 (s, 2H),



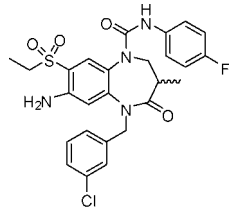
compound **16c**

6.920–7.166 (m, 6H), 7.231–7.648 (m, 8H), 7.902 (s, 1H), 8.031 (s, 1H), 9.349 (s, 1H).



compound **16d**

7-Amino-5-(3-chlorobenzyl)-8-(ethylsulfonyl)-*N*-(4-fluorophenyl)-3-methyl-4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-1-carboxamide. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.005 (d, 3H, J = 6.3 Hz), 1.140 (t, 3H, J = 7.2 Hz), 2.779–2.866 (m, 1H), 3.194 (q, 2H, J = 7.2 Hz), 3.519–3.580 (m, 1H), 3.965–4.047 (m, 1H), 4.875 (d, 1H, J = 16.5 Hz), 4.977 (d, 1H, J = 16.5 Hz), 6.269 (brs, 2H), 6.853 (s, 1H), 7.014–7.145 (m, 2H), 7.145–7.212 (m, 1H), 7.226–7.275 (m, 3H), 7.275–7.383 (m, 2H), 7.376 (s, 1H), 8.069 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 6.956, 12.964, 35.857, 47.766, 50.603, 55.440, 110.595, 114.563, 116.000, 121.870, 122.412, 124.926, 126.272, 126.772, 130.102, 130.857, 133.161, 136.006, 140.309, 146.946, 147.766, 154.246, 157.590, 173.574.



compound **18**

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