Solution-Phase Parallel Synthesis of 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones

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Practical and efficient parallel methods have been developed for the synthesis of 7,8-disubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones and 3,7,8-trisubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones. This benzothiazepin-4(5*H*)-one skeleton possesses three or four diversity points. Furthermore, three novel tricycles integrating a benzothiazepin-4(5*H*)-one scaffold with other privileged structures, such as benzimidazole, benzimidazolone, and thio-benzimidazole, were also developed. The synthetic strategy provides an efficient way to access the benzothiazepinone core, starting from commercially available 1,5-difluoro-2,4-dinitrobenzene (DFDNB), and also allows further derivation of the strategically anchored functionalities.

Introduction

The benzothiazepine core has long been recognized as a "privileged structure" for drug design. It is well documented that benzothiazepine derivatives are of particular interest for drug discovery because they are known to elicit a broad spectrum of biological activities. Some of them have been used clinically for the treatment of cardiovascular disorders, such as diltiazem,[1] nictiazem,[2] and clentiazem,[3] or as antidepressants, such as thiazesim[4] (Figure 1). Thus, the efficient preparation of diversified 1,5-benzothiazepin-4(5*H*)-one library is of considerable interest for both medicinal and organic chemists.

1,5-Difluoro-2,4-dinitrobenzene (DFDNB) is a protein cross-linker and also a versatile reagent for a diverse 1,5-dialkylamino-2,4-dinitrobenzene library synthesis.[5] Our group successfully launched a "scaffold-directed" project to develop various benzofused chemical libraries, such as 2-hydroxyquinoxalines,[6] benzimidazoles,[7] imidazoquinoxalinols,[8] indolin-2-ones,[9] benzo[1,4]oxazin-3-ones,[10] and benzo[1,4]-thiazin-3-ones,[11] using DFDNB as the starting material. Herein, we wish to report a novel and efficient solution-phase synthetic route to generate 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**A** and **B**) and 3,7,8-trisubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**C** and **D**), which allows the preparation of a wide variety of compounds in high purity. Furthermore, three novel tricyclic scaffolds are also developed, which are an integration of the 1,1-dioxo-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one core with benzimidazole, benzimidazolone, and thio-benzimidazole (**E**−**G**) (Figure 2). 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.

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Results and Discussion

The synthetic route to the chemical scaffold of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**I**) is depicted in Scheme 1. From **1**, two fluorine atoms were quantitatively substituted by the 3-mercapto-propionic acid ethyl ester and, subsequently, by amines to give compound **3** in the presence of an organic base, such as diisopropylethylamine (DIPEA), triethylamine (TEA), or *N*-methylmorpholine (NMM), as previously reported.[5] Unexpected side products were not observed in these two reaction steps when equivalent reactants were used.

Compound **3** was reduced by stannous chloride in the presence of hydrochloric acid (38%) to yield **4**, which was further hydrolyzed to give the corresponding compound **5** after removal of the Sn salt by 30% NaOH. Compound **5** then was cyclized to afford the desired benzothiazepine scaffold **I** (Scheme 1) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) in high yield and excellent purity. Excess EDC and the byproduct 1-(3-(dimethylamino)propyl)-3-ethylurea (EDU) from EDC were easily removed through the extraction against water.

We have attempted to obtain the corresponding sulfone of **I** (**II**) directly for an additional diversity point. Unfortunately, sulfide **I** was very unstable under the various harsh oxidation conditions tested. Therefore an alternative method was developed (Scheme 2). UHP (adduct of hydrogen peroxide and urea) has been optimized in our group to prepare aromatic sulfones from sulfides.[11] Treatment of compound **3** with UHP readily provided the corresponding sulfone **6**. Then the reduction of the two nitro groups of **6** with Pd/C−$HCOONH_4$ provided **7** at room temperature in 10 min. Hydrolysis of **7** by LiOH was necessary to give the desired **8**. Cyclization of **8** with EDC smoothly afforded the benzothiazepinone **II**.

I and **II** were further reacted with aldehydes, anhydrides, isocyanates, isothiocyanates, and sulfonyl chlorides to generate the corresponding secondary amines, amides, ureas,

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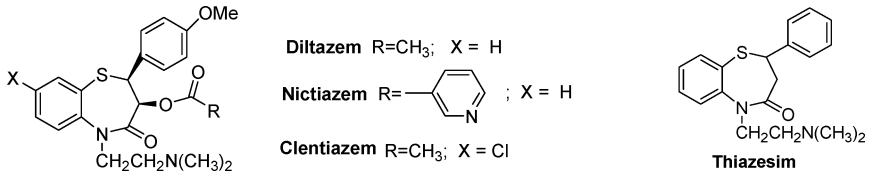


Figure 1. Derivatives of 1,5-benzothiazepin-4(*5H*)-one on the medicine market.

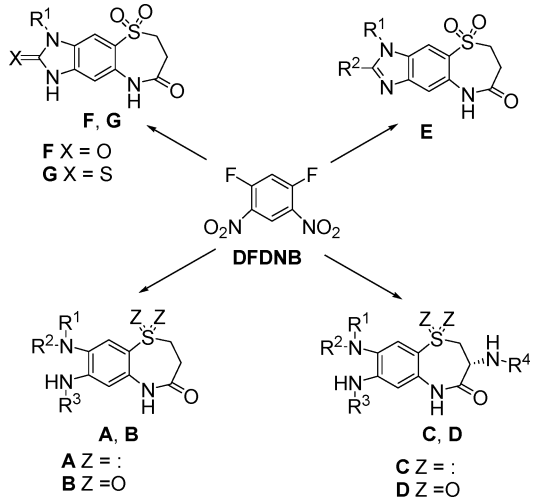


Figure 2. Generated 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones, 3,7,8-trisubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones, and three novel diverse benzofused scaffolds from DFDNB.

thioureas, and sulfonamides, respectively (Scheme 3). We found that the 7-amino group of **II** is less prone to reaction because of the electron-withdrawing effect of sulfone group. Extension of the reaction time or elevation of the reaction temperature was necessary to obtain the anticipated derivatives of **II**. Typical compounds were synthesized and characterized by LC-MS and ^{1}H or ^{13}C NMR (Table 1).

The third diversity point at the 3-position of **I** or **II** was introduced when Fmoc-N^{α}-cysteine acid was used (Scheme 4). Intermediate **10** was obtained from **1** after two substitution steps. Oxidation of sulfide **10** by UHP gave the corresponding sulfone **11**. Compounds **10** and **11** were reduced to the corresponding amines **12** and **13** by stannous chloride. Noticeably, Pd/C−$HCOONH_4$ is not a proper reducing agent for this reaction because the Fmoc group was able to be removed by Pd/C−$HCOONH_4$. Compounds **12** and **13** were readily converted into the benzothiazepinones **III** and **IV** in THF/H_2O (v/v = 1:1) through intramolecular amide bond formation in the aid of EDC.

The free 7-aromatic amino group of **III** and **IV** were then acylated by anhydride or isocyanate to introduce the third diversity point. Typical compounds of **14** and **15** (Scheme 5) were synthesized and were characterized by LC-MS, HRMS, and ^{1}H NMR (Table 2).

The remaining steps in the synthetic sequence involved further functionalization of the exocyclic amino group of the 1,5-benzothiazepin-4(*5H*)-one template. This includes Fmoc removal from **14** and **15** by piperidine treatment and derivation of the resulting primary amines **16** and **17** with anhydrides, isocyanates, isothiocyanates, and sulfonyl chlorides to generate the corresponding amides, ureas, thioureas, and sulfonamides, respectively (Scheme 5). We also attempted to use insoluble cross-linked polystyrene reagents bearing piperazino functionality **18** as scavenging agent.[12] Using this method, we obtained the pure products **16** and **17** directly without further purification. However, it required a long reaction time and consumed large amount of resin. For this reason, the piperidine was finally selected to remove the Fmoc group directly, followed by a silica gel purification step.

Typical compounds were characterized by LC-MS, HRMS, and ^{1}H NMR (Table 2).

Scheme 6 depicts the synthetic routes to three novel tricyclic scaffolds. If a primary amine was used in the substitution of compound **2**, the intermediate **II** containing a secondary amino group at 8-position could be obtained. The presence of a hydrogen atom at the 8-amino group encouraged us to develop the novel tricyclic scaffolds. The reaction of **II** with excess aldehyde in the presence of a weakly acidic solution (5%) at room temperature gave the benzimidazole **E** in high yield. When the intermediate **II** was treated with excess triphosgene or carbon disulfide, novel scaffolds **F** and **G** were obtained in the presence of triethylamine. Typical compounds are listed in Tables 3 and 4. Unfortunately, compound **19** was too unstable to obtain scaffold **I** under the various conditions tested. Thus, the further construction of tricycles based on **I** was not successful in this study.

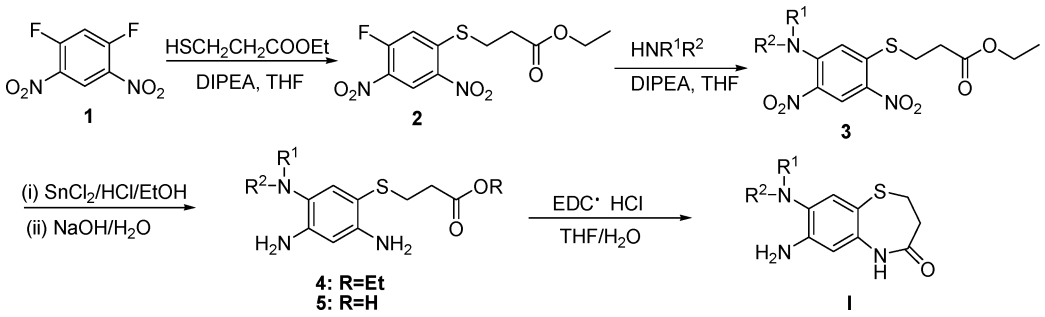
Conclusion

In conclusion, we developed efficient, high-yielding solution-phase routes to generate 7,8-disubstitued and 3,7,8-trisubstitued 1,5-benzothiazepin-4(5*H*)-ones from DFDNB. Furthermore, three novel tricycles containing benzothiazepin-4(5*H*)-one scaffolds with benzimidazole, benzimidazolone, and thio-benzimidazole were developed. 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.

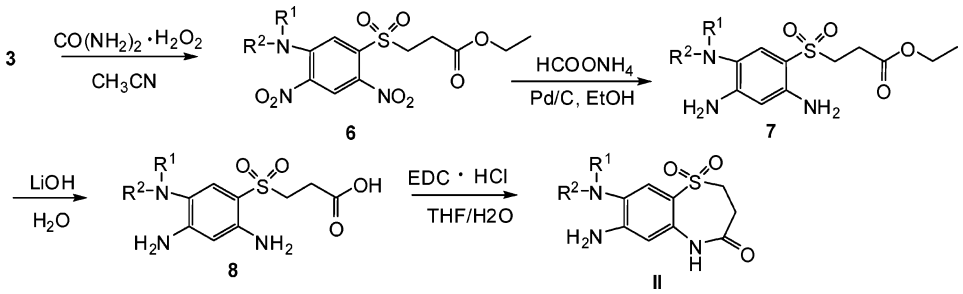
Experimental Section

All chemical reagents were purchased from Acros Organics (Geel, Belgium) and were used without further purification. Tetrahydrofuran (THF) was dried over molecular sieves and redistilled from sodium before used. 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 hander. The column employed was a Kromasil C18 column (4.6 μm, 4.6 mm × 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 5 min at a 1 mL/min. The UV detection was carried out at a UV wavelength of 254 nm. Automatic LC-MS analysis was performed on a Ther-

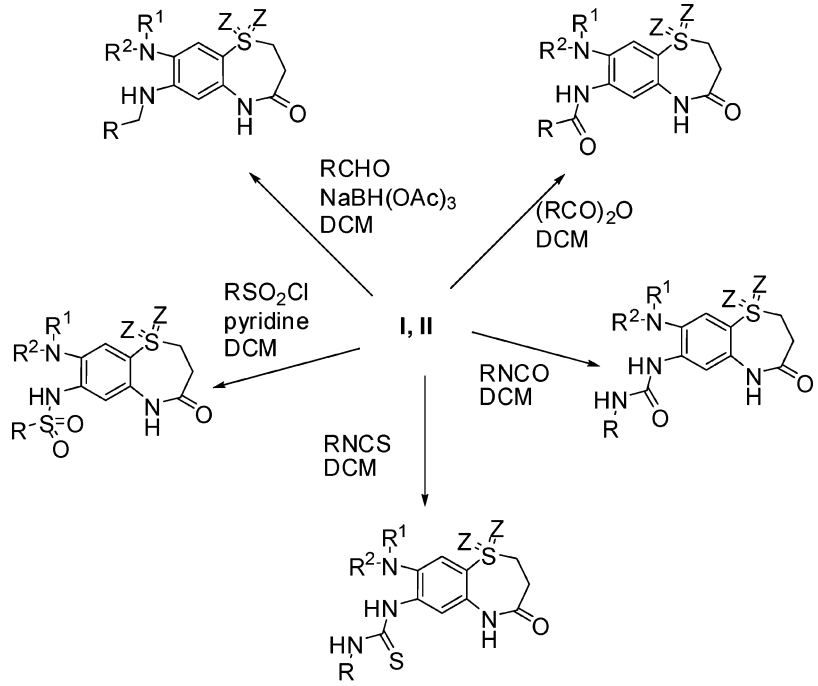
Scheme 1. Synthetic Route to 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones



Scheme 2. Synthetic Route to 1,1-Dioxo-7,8-substituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones



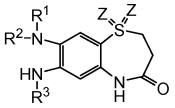
Scheme 3. Derivation of **I** and **II** at 7-Aromatic Amino Group



moFinnigan 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 above. Five percent of the eluent was split into the MS system. Mass spectra were recorded in either positive or 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 $\times$ 30 mm) at a flow of 0.40 mL/min. The solvent was MeOH/water (75:25 (v/v)), containing 5 mmol/L ammonium formate. The ion source is electrospray ionization (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 GmbH parallel synthesizer.

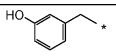
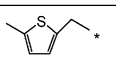
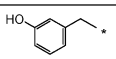
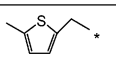
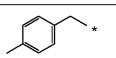
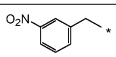
General Procedure for the Synthesis of Intermediate 2. A solution of 1.0 equiv of 3-mercapto-propionic acid ethyl ester in 30 mL of THF was added dropwise to a magnetically stirred solution of 1.0 equiv (5.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene and 1.0 equiv of diisopropylethylamine (DIPEA) in 50 mL of THF. The reaction mixture was continuously stirred for an additional 1 h at room temperature. After the solvent was evaporated under reduced

Table 1. Molecular Weights and HPLC Purities for the Representative 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones (**A** and **B**)



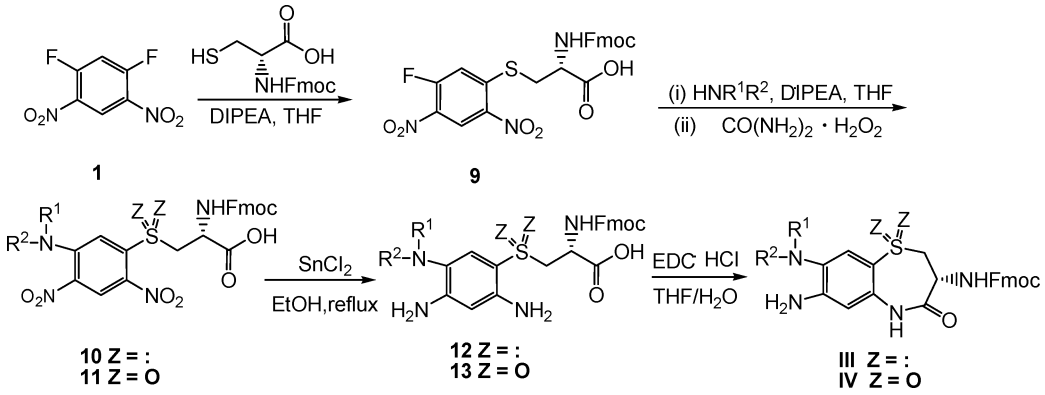
Entry	Z	R^1	R^2	R^3	HPLC purity[a] (%)	MS (found)	MW (calcd)
A1	:			H	100.0	294.1	293
A2	:		— *	H	99.5	306.1	305
A3	:			H	100.0	278.1	277
A4	:			H	100.0	263.2	262
A5	:				98.3	361.8	361
A6	:				100.0	336.2	335
A7	:				100.0	431.2	430
A8	:				99.2	434.0	433
A9	:				98.9	378.2	377
A10	:				100.0	412.1	411
A11	:		— *		99.6	424.2	423
A12	:		— *		100.0	362.1	361
A13	:		— *		100.0	443.1	442
A14	:				97.6	388.0	387
A15	:				100.0	334.2	333
A16	:				96.4	413.1	412
A17	:				98.9	488.1	487
A18	:				100.0	504.0	503
A19	:				99.1	554.2	553
B1	O			H	99.2	326.1	325
B2	O			H	96.7	310.1	309
B3	O			H	100.0	311.8	311
B4	O			H	98.4	295.9	295
B5	O				100.0	382.1	381
B6	O				99.7	410.1	409
B7	O				98.0	394.2	393
B8	O				99.4	430.1	429
B9	O				97.1	450.1	449

Table 1 (Continued)

Entry	Z	R^1	R^2	R^3	HPLC purity[a] (%)	MS (found)	MW (calcd)
B10	O				100.0	432.1	431
B11	O				100.0	435.9	435
B12	O				97.5	444.1	443
B13	O				96.3	448.0	447
B14	O				98.7	442.1	441
B15	O				97.7	473.1	472

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

Scheme 4. Synthetic Route to 3,7,8-Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones



pressure, water was added to precipitate **2**. The desired intermediate **2** then was collected by filtration and washed thoroughly with water. For a typical compound, for example, 3-(5-fluoro-2,4-dinitro-phenylsulfanyl)-propionic acid ethyl ester, 1.574 g of yellow powder was gained in 99% yield with an HPLC purity of >99%. ESI-MS: *m*/*z* 317.1 $(M - H)^+$.

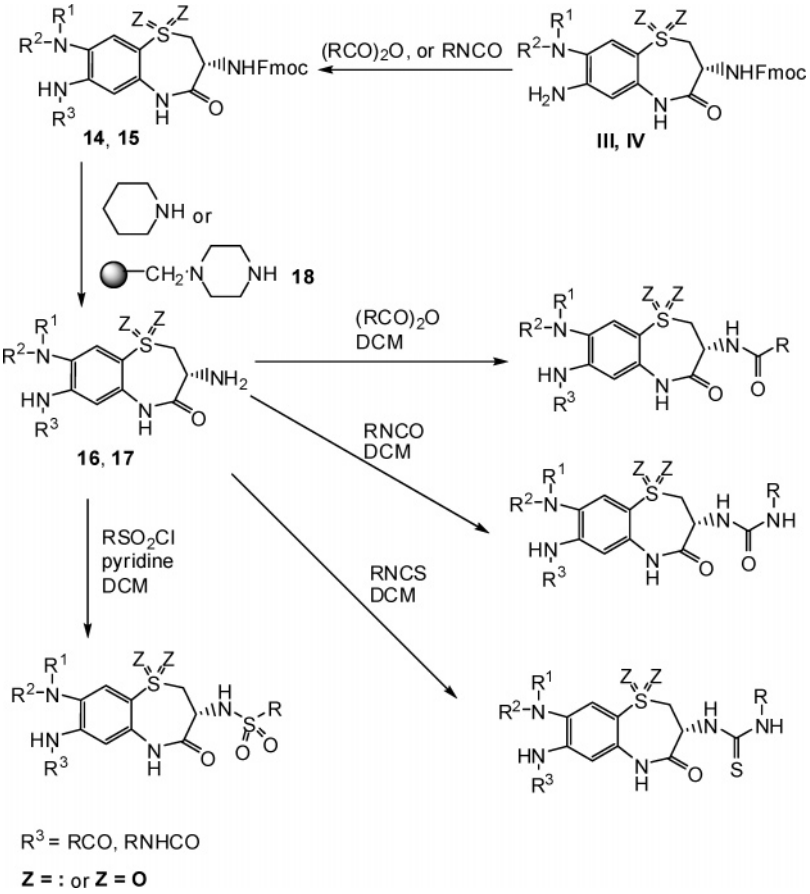
General Procedure for the Synthesis of Intermediate 3. One equivalent of of amine was added to a magnetically stirred solution of 1.0 equiv (4.0 mmol) of intermediate **2** and 1.0 equiv of DIPEA in 50 mL THF. The reaction mixture was continuously stirred for 4 h at room temperature. The reaction mixture was evaporated in vacuo to dryness. Thirty milliliters of water was added to precipitate **3** as a yellow solid. Then compound **3** was collected after it was thoroughly washed with water. For a typical compound, for example, 3-(5-dipropylamino-2,4-dinitro-phenylsulfanyl)-propionic acid ethyl ester, 1.505 g of yellow powder was obtained in 94% yield with an HPLC purity of >99%. ESI-MS: *m*/*z* 398.1 $(M - H)^-$.

General Procedure for the Synthesis of Intermediate 5. Compound **3** (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 2 h. The reaction mixture then was slowly and carefully poured into a cold 30% NaOH solution (60 mL). The pH value must be carefully adjusted to 10. The resulting mixture was extracted with DCM (3 × 30·mL). The organic layers were combined and concentrated under reduced pressure to give crude compound **5**. For a typical compound, for example, 3-(2,4-diamino-5-dipropylamino-phenylsulfanyl)-propionic acid, 750 mg of pale powder was obtained in 80% yield with an HPLC purity of >96%. ESI-MS: *m*/*z* 312.2 $(M + H)^+$.

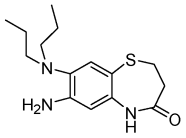
General Procedure for the Synthesis of I. EDC·HCl (6 mmol) was added to a solution of **5** (2.0 mmol) in 40 mL of THF/H_2O (1:1, v/v), and the mixture was allowed to react for 3 h until it was complete; completion was monitored by a fast LC-MS system. The mixture was concentrated in vacuo to remove THF and was extracted with EtOAc (3 × 50 mL). The organic phase was dried over $MgSO_4$ and purified by silica gel column chromatography, eluting with ethyl acetate/petroleum ether. For a typical compound, for example, **A1**, 440 mg of pale powder was obtained in 75% yield with an HPLC purity of >99%.

7-Amino-8-dipropylamino-2,3-dihydro-5*H*-benzo[*b*][1,4]-thiazepin-4-one (A1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.822

Scheme 5. Modification of **III** and **IV** at 7- and 3-Amino Groups

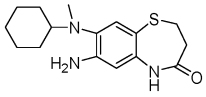


(t, 6H, J = 7.2 Hz), 1.345−1.468 (m, 4H), 2.598 (t, 2H, J = 6.9 Hz), 2.772−2.822 (t, 4H, J = 7.2 Hz), 3.345 (t, 2H, J = 6.9 Hz), 4.283 (brs, 2H), 6.469 (s, 1H), 7.177 (s, 1H), 8.300 (brs, 1H). ^{13}C NMR (75 MHz): δ 11.681, 20.493, 33.615, 34.558, 56.008, 109.111, 113.357, 129.792, 135.877, 138.311, 145.660, 174.400.



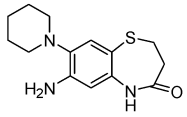
compound **A1**

7-Amino-8-(cyclohexyl-methyl-amino)-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.037−1.389 (m, 4H), 1.584−1.621 (m, 2H), 1.760−1.781 (m, 4H), 2.501−2.573 (m, 1H), 2.604 (s, 3H), 2.607 (t, 2H, J = 6.9 Hz), 3.353 (t, 2H, J = 6.9 Hz), 4.207 (brs, 2H), 6.448 (s, 1H), 7.180 (s, 1H), 7.615 (brs, 1H).



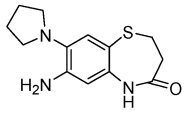
compound **A2**

7-Amino-8-piperidin-1-yl-2,3-dihydro-5*H*-benzo[*b*][1,4]-thiazepin-4-one (A3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.505−1.583 (m, 2H), 1.653−1.724 (m, 4H), 2.586 (t, 2H, J = 6.9 Hz), 2.792 (brs, 4H), 3.345 (t, 2H, J = 6.9 Hz), 4.177 (brs, 2H), 6.468 (s, 1H), 7.125 (s, 1H), 8.265 (s, 1H). ^{13}C NMR (75 MHz): δ 23.741, 26.285, 33.194, 34.247, 52.292, 108.772, 113.265, 126.232, 137.387, 138.229, 142.933, 173.982.



compound **A3**

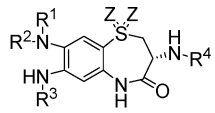
7-Amino-8-pyrrolidin-1-yl-2,3-dihydro-5*H*-benzo[*b*][1,4]-thiazepin-4-one (A4). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.821 (brs, 4H), 2.344 (t, 2H, J = 6.9 Hz), 2.914 (brs, 4H), 3.211 (t, 2H, J = 6.9 Hz), 5.032 (brs, 2H), 6.397 (s, 1H), 6.922 (s, 1H), 9.408 (s, 1H).

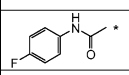
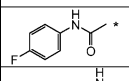
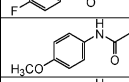
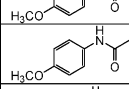
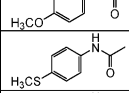
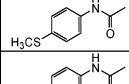
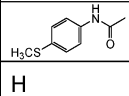
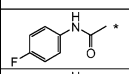
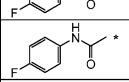


compound **A4**

General Procedure for the Synthesis of Intermediate 6. UHP (18 mmol) and trifluorous acetic anhydride (10 mmol) in 30 mL of acetonitrile were slowly added under stirring to a solution of **3** (3 mmol) in acetonitrile (30 mL) at 0 °C. The oxidative progress was then monitored by a

Table 2. Molecular Weights and HPLC Purities of the Representative 3,7,8-Trisubstituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones (**C** and **D**)



Entry	Z	R^1	R^2	R^3	R^4	HPLC purity[a] (%)	HRMS (M + H^+)	
							found	calcd
C1	:		— *	H	Fmoc	99.0	543.2319	543.2430
C2	:		— *		Fmoc	100.0	639.2252	639.2253
C3	:		— *		Fmoc	100.0	680.2702	680.2703
C4	:			H	Fmoc	99.6	530.2413	530.2430
C5	:				Fmoc	98.9	668.2703	668.2707
C6	:				Fmoc	100.0	680.2901	680.2907
C7	:				H	98.7	458.2222	458.2226
C8	:				Fmoc	99.1	696.2675	696.2678
C9	:				H	100.0	474.2041	474.2000
C10	:					99.5	570.1886	570.1820
C11	:					98.9	611.2269	611.2274
D1	O		— *	H	Fmoc	100.0	575.2300	575.2328
D2	O		— *		H	99.4	490.1922	490.1924
D3	O		— *			100.0	586.1780	585.1747
D4	O		— *		Fmoc	97.9	671.2155	671.2151
D5	O		— *		H	100.0	449.1407	449.1470
D6	O		— *			100.0	588.1320	588.1325
D7	O		— *			98.9	601.1413	601.1405

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

fast LC-MS analysis. After completion of the oxidation, the mixture was diluted with water (30 mL) and extracted with DCM (3 × 30 mL). The DCM layers were combined, washed with saturated NaCl solution (1 × 30 mL), dried over anhydrous $MgSO_4$. The solid then was filtered, and the filtrate was concentrated in vacuo to obtain solid of **6**. For a typical compound, for example, 3-(5-dipropylamino-2,4-dinitro-benzenesulfonyl)-propionic acid ethyl ester, 1.260 g of yellow powder was obtained in 95% yield with an HPLC purity of >99%. ESI-MS: *m*/*z* 432.1 $(M + H)^+$.

General Procedure for the Synthesis of Intermediate 7. $HCOONH_4$ (30 mmol) and 0.2 g of 10% Pd/C were added to a solution of 3.0 mmol of substituted **6** in 50 mL of ethanol under stirring. The reaction mixture turned from yellow to red and finally colorless in 30 min at room temperature. The catalyst and excess $HCOONH_4$ were filtered off. The filtrate was concentrated in vacuo to yield **7**. For a typical compound, for example, 3-(2,4-diamino-5-dipropylamino-benzenesulfonyl)-propionic acid ethyl ester, 900 mg of pale powder was obtained in 85% yield with an HPLC purity of >96%. ESI-MS: *m*/*z* 372.2 $(M + H)^+$.

General Procedure for the Synthesis of II. $LiOH \cdot H_2O$ (1.05 g) in 20 mL of water was added under stirring to a solution of 2.0 mmol of **7** in 20 mL of THF. The reaction mixture was continuously stirred for 1 h at room temperature. The pH value was adjusted to 7.0 with 2 N HCl. The

Scheme 6. Synthetic Route to Three Novel Tricyclic Scaffolds

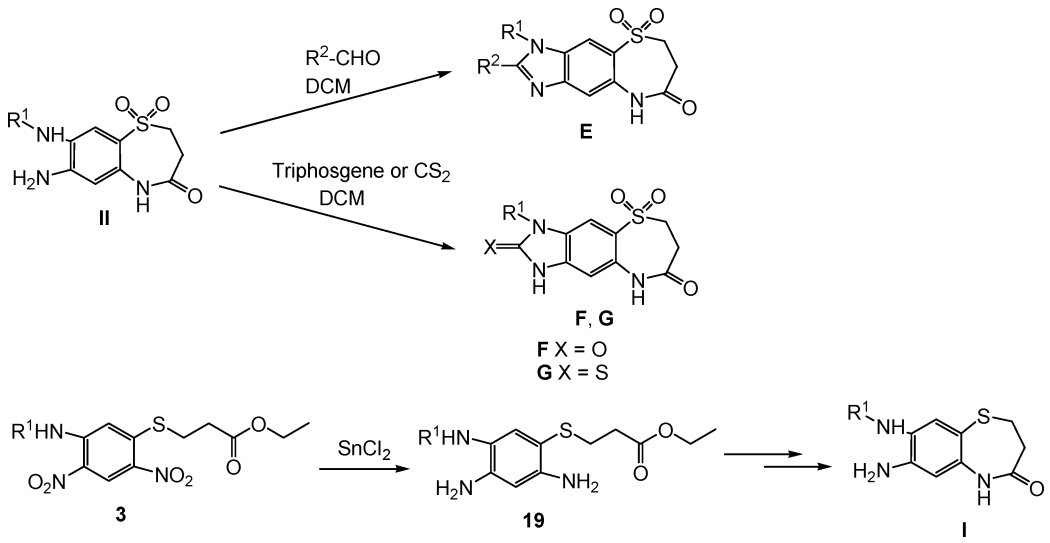
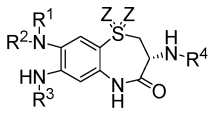
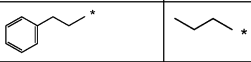
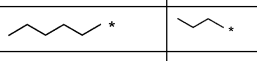
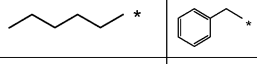
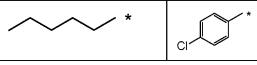


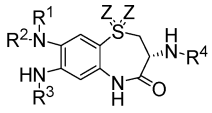
Table 3. Molecular Weights and HPLC Purities for the Representative Novel Tricyclic Scaffold **(E**)

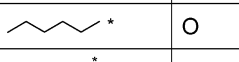
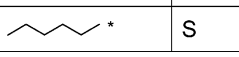


Entry	R^1	R^2	HPLC purity[a](%)	MS (found)	MS (calcd)
E1			99.3	398.2	397
E2			100.0	466.1	465
E3			99.1	364.2	363
E4			100.0	412.3	411
E5			100.0	432.2	431

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

Table 4. Molecular Weights and HPLC Purities for the Representative Novel Tricyclic Scaffold (**F** and **G**)



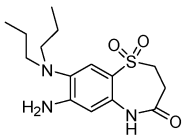
Entry	R^1	X	HPLC Purity[a](%)	MS (found)	MS (calcd)
F1		O	100.0	372.1	371
F2		O	97.8	338.1	337
G1		S	98.6	388.2	387
G2		S	100.0	354.0	353

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

resulting solution was analyzed by HPLC under UV 254 wavelength, which showed a single HPLC peak with an anticipated molecular weight of *m*/*z* 344.2 $(M + H)^+$ for 3-(2,4-diamino-5-dipropylamino-benzenesulfonyl)-propionic acid, for example. This solution was directly added to EDC·HCl (6 mmol), and the mixture was allowed to react

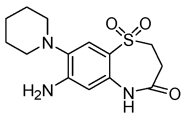
for an additional 3 h until the completion, as monitored by a fast LC-MS system. The mixture was concentrated in vacuo to remove THF and was extracted with EtOAc (3 × 50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with ethyl acetate/petroleum ether. For a typical compound, for example, **B1**, 490 mg of pale powder was obtained in 76% yield with an HPLC purity of >99%.

7-Amino-8-dipropylamino-1,1-dioxo-1,2,3,5-tetrahydro-1λ⁶-benzo[*b*][1,4]thiazepin-4-one (B1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.800 (t, 6H, J = 7.2 Hz), 1.311−1.383 (m, 4H), 2.518 (t, 2H, J = 6.9 Hz), 2.761 (t, 4H, J = 7.2 Hz), 3.664 (t, 2H, J = 6.9 Hz), 5.887 (brs, 2H), 6.396 (s, 1H), 7.310 (s, 1H), 9.862 (brs, 1H). ^{13}C NMR (75 MHz): δ 11.573, 19.771, 30.121, 54.958, 56.922, 107.508, 116.205, 121.995, 131.854, 135.719, 150.838, 170.844.



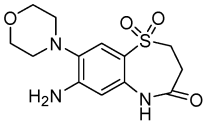
compound **B1**

7-Amino-1,1-dioxo-8-piperidin-1-yl-1,2,3,5-tetrahydro-1λ⁶-benzo[*b*][1,4] thiazepin-4-one (B2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.505−1.586 (m, 2H), 1.703 (brs, 4H), 2.744 (t, 2H, J = 7.2 Hz), 2.816 (brs, 4H), 3.706 (t, 2H, J = 7.2 Hz), 4.720 (brs, 2H), 6.455 (s, 1H), 7.541 (s, 1H), 8.262 (s, 1H).



compound **B2**

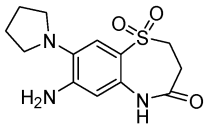
7-Amino-8-morpholin-4-yl-1,1-dioxo-1,2,3,5-tetrahydro-1λ⁶-benzo[*b*][1,4]thiazepin-4-one (B3). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.450 (t, 2H, J = 7.2 Hz), 2.690 (brs, 4H), 3.657 (t, 2H, J = 7.2 Hz), 3.705 (brs, 4H), 5.897 (brs, 1H), 6.354 (s, 1H), 7.184 (s, 1H), 9.814 (s, 1H).



compound **B3**

7-Amino-1,1-dioxo-8-pyrrolidin-1-yl-1,2,3,5-tetrahydro-1λ⁶-benzo[*b*][1,4]thiazepin-4-one (B4). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.624 (brs, 4H), 2.300 (t, 2H, J = 6.9 Hz), 2.716 (brs, 4H), 3.432 (t, 2H, J = 7.2 Hz), 5.583 (brs, 2H), 6.162 (s, 1H), 6.995 (s, 1H), 9.582 (s, 1H).

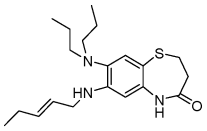
Derivation of I and II at 7-Aromatic Amino Group. Method 1. A solution of **I** or **II** (0.1 mmol) in 5 mL of anhydrous DCM was added to a mixture of aldehydes (0.1 mmol), $NaBH(OAc)_3$ (0.2 mmol), and glacetic acid (100 μL). The reaction mixture was stirred mechanically on an H + P



compound **B4**

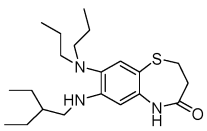
Labortechnik GmbH parallel synthesizer at 45 °C for at least 12 h. Chemical conversion was monitored by LC-MS analysis. After the reaction was complete, the solution was evaporated in vacuo to dryness. The crude residue was dissolved in 15 mL of DCM and then was washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL). After it was completely dried over anhydrous Na_2SO_4, the filtrate was concentrated in vacuo to obtain the crude product. The final products were characterized after chromatography purification on silica gel. The yields range from 70 to 90%.

8-Dipropylamino-7-pent-2-enylamino-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.849 (t, 6H, J = 7.2 Hz), 0.990 (t, 3H, J = 7.2 Hz), 1.337−1.435 (m, 4H), 2.014−2.085 (m, 2H), 2.604 (t, 2H, J = 6.9 Hz), 2.753 (t, 4H, J = 7.2 Hz), 3.350 (t, 2H, J = 6.9 Hz), 3.672 (brs, 2H), 5.244 (brs, 1H), 5.474−5.529 (m, 1H), 5.687−5.700 (m, 1H), 6.251 (s, 1H), 7.263 (s, 1H), 7.294 (s, 1H).



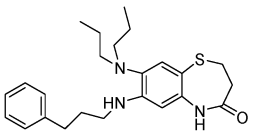
compound **A5**

8-Dipropylamino-7-(2-ethyl-butylamino)-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A9). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.849 (t, 6H, J = 7.2 Hz), 0.916 (t, 6H, J = 7.2 Hz), 1.366−1.458 (m, 8H), 1.482−1.540 (m, 1H), 2.608 (t, 2H, J = 6.9 Hz), 2.781 (t, 4H, J = 7.2 Hz), 2.876 (d, 2H, J = 5.4 Hz), 3.348 (t, 2H, J = 6.9 Hz), 5.212 (brs, 1H), 6.234-(s, 1H), 7.149 (s, 1H), 7.351 (s, 1H).



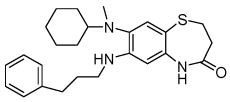
compound **A9**

8-Dipropylamino-7-(3-phenyl-propylamino)-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.859 (t, 6H, J = 7.2 Hz), 1.342−1.464 (m, 4H), 1.900−1.996 (m, 2H), 2.598 (t, 2H, J = 6.9 Hz), 2.707−2.798 (m, 6H), 3.098−3.113 (m, 2H), 3.348 (t, 2H, J = 6.9 Hz), 5.214 (brs, 1H), 6.156 (s, 1H), 7.157−7.330 (m, 7H).



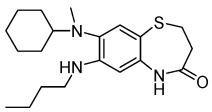
compound **A10**

8-(Cyclohexyl-methyl-amino)-7-(3-phenyl-propylamino)-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A11). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.079−1.375 (m, 4H), 1.600−1.618 (m, 2H), 1.701−1.772 (m, 4H), 1.936−2.007 (m, 2H), 2.577 (s, 3H), 2.625 (m, 3H), 2.738 (t, 2H, J = 7.2 Hz), 3.079−3.099 (m, 2H), 3.352 (t, 2H, J = 6.9 Hz), 5.025 (brs, 1H), 6.166 (s, 1H), 7.144 (s, 1H), 7.190−7.332 (m, 6H).



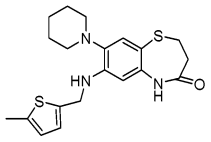
compound **A11**

7-Butylamino-8-(cyclohexyl-methyl-amino)-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A12). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.970 (t, 3H, J = 7.2 Hz), 1.113−1.328 (m, 4H), 1.379−1.504 (m, 2H), 1.603−1.625 (m, 4H), 1.755 (brs, 4H), 2.570 (s, 3H), 2.607 (t, 2H, J = 6.9 Hz), 2.610−2.630 (m, 1H), 3.069 (t, 2H, J = 6.3 Hz), 3.352 (t, 2H, J = 6.9 Hz), 4.944 (brs, 1H), 6.239 (s, 1H), 7.134 (s, 1H), 7.312-(s, 1H).



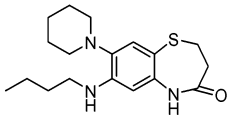
compound **A12**

7-[(5-Methyl-thiophen-2-ylmethyl)-amino]-8-piperidin-1-yl-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A14). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.677 (brs, 6H), 2,451 (s, 3H), 2.583 (t, 2H, J = 6.9 Hz), 2.791 (brs, 4H), 3.349 (t, 2H, J = 6.9 Hz), 4.416 (s, 2H), 5.298 (brs, 1H), 6.315 (s, 1H), 6.605 (d, 2H, J = 3.0 Hz), 6.768 (d, 2H, J = 3.0 Hz), 7.136 (s, 1H), 7.258 (brs, 1H).



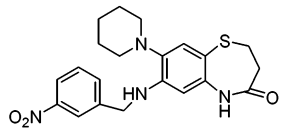
compound **A14**

7-Butylamino-8-piperidin-1-yl-2,3-dihydro-5*H*-benzo-[*b*][1,4]thiazepin-4-one (A15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.976 (t, 3H, J = 7.2 Hz), 1.403−1.495 (m, 4H), 1.672 (brs, 6H), 2.593 (t, 2H, J = 6.9 Hz), 2.805 (brs, 4H), 3.073 (t, 2H, J = 6.9 Hz), 3.349 (t, 2H, J = 6.9 Hz), 6.251 (s, 1H), 7.106 (s, 1H), 7.353 (s, 1H).



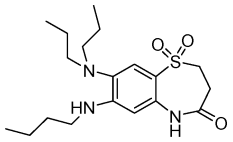
compound **A15**

7-(3-Nitro-benzylamino)-8-piperidin-1-yl-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (A16). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.718 (brs, 6H), 2.557 (t, 2H, J = 6.9 Hz), 2.804 (brs, 4H), 3.344 (t, 2H, J = 6.9 Hz), 4.467 (s, 2H), 5.535 (brs, 1H), 6.116 (s, 1H), 7.188 (s, 1H), 7.537 (t, 1H, J = 7.8 Hz), 7.664 (d, 1H, J = 7.8 Hz), 8.150 (d, 1H, J = 7.8 Hz), 8.206 (s, 1H).



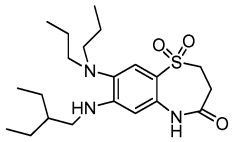
compound **A16**

7-Butylamino-8-dipropylamino-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.857 (t, 6H, J = 7.2 Hz), 0.976 (t, 3H, J = 7.2 Hz), 1.384−1.478 (m, 6H), 1.595−1.655 (m, 2H), 2.751−891 (m, 6H), 3.144 (brs, 2H), 3.717 (t, 2H, J = 6.9 Hz), 5.701 (brs, 1H), 6.215 (s, 1H), 7.571 (s, 1H), 7.775 (s, 1H).



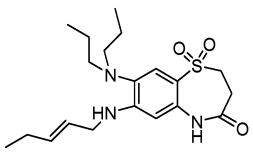
compound **B5**

8-Dipropylamino-7-(2-ethyl-butylamino)-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B6). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.849 (t, 6H, J = 7.2 Hz), 0.926 (t, 6H, J = 7.2 Hz), 1.389−1.436 (m, 8H), 1.524−1.543 (m, 1H), 2.751−87 (m, 6H), 3.048 (t, 2H, J = 5.4 Hz), 3.713 (t, 2H, J = 6.9 Hz), 5.743 (brs, 1H), 6.221 (s, 1H), 7.563 (s, 1H), 7.944 (s, 1H).



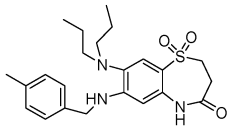
compound **B6**

8-Dipropylamino-1,1-dioxo-7-pent-2-enylamino-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.860 (t, 6H, J = 7.2 Hz), 0.997 (t, 3H, J = 7.2 Hz), 1.384−1.412 (m, 4H), 2.057−2.101 (m, 2H), 2.771−2.796 (m, 6H), 3.698−3.744 (m, 4H), 5.450−5.502 (m, 1H), 5.701−5.754 (m, 1H), 5.759 (brs, 1H), 6.217 (s, 1H), 7.586 (s, 2H).



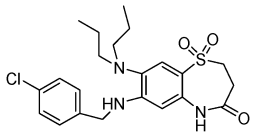
compound **B7**

8-Dipropylamino-7-(4-methyl-benzylamino)-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B8). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.840 (t, 6H, J = 7.2 Hz), 1.318−1.411 (m, 4H), 2.351 (s, 3H), 2.740 (t, 2H, J = 6.9 Hz), 2.764−2.814 (m, 4H), 3.699 (t, 2H, J = 6.9 Hz), 4.328 (d, 2H, J = 5.7 Hz), 6.200 (s, 1H), 7.173 (brs, 4H), 7.599 (s, 1H).



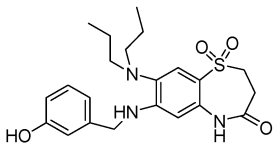
compound **B8**

7-(4-Chloro-benzylamino)-8-dipropylamino-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B9). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.872 (t, 6H, J = 7.2 Hz), 1.318−1.416 (m, 4H), 2.738 (t, 2H, J = 6.9 Hz), 2.764−2.821 (m, 4H), 3.701 (t, 2H, J = 6.9 Hz), 4.354 (d, 2H, J = 5.7 Hz), 6.162 (s, 1H), 7.228 (d, 2H, J = 8.1 Hz), 7.338 (d, 2H, J = 8.1 Hz), 7.618 (s, 1H), 7.729 (s, 1H).



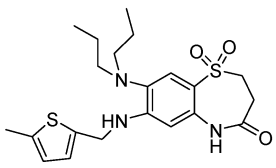
compound **B9**

8-Dipropylamino-7-(3-hydroxy-benzylamino)-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.934 (t, 6H, J = 7.2 Hz), 1.318−1.426 (m, 4H), 2.712−2.800 (m, 6H), 3.579 (t, 2H, J = 6.9 Hz), 4.397 (brs, 2H), 6.223 (brs, 1H), 6.438 (s, 1H), 6.722−6.783 (m, 3H), 7.179 (s, 1H), 7.594 (s, 1H), 8.473 (s, 1H).



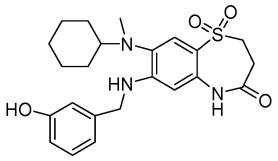
compound **B10**

8-Dipropylamino-7-[(5-methyl-thiophen-2-ylmethyl)-amino]-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]-thiazepin-4-one (B11). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.849 (t, 6H, J = 7.2 Hz), 1.315−1.424 (m, 4H), 2.449 (s, 3H), 2.734 (t, 2H, J = 6.9 Hz), 2.782 (brs, 4H), 3.714 (t, 2H, J = 6.9 Hz), 4.479 (brs, 2H), 6.284 (s, 1H), 6.605 (d, 1H, J = 2.1 Hz), 6.765 (d, 1H, J = 2.1 Hz), 7.604 (s, 1H).



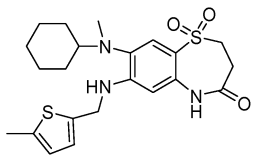
compound **B11**

8-(Cyclohexyl-methyl-amino)-7-(3-hydroxy-benzylamino)-2,3-dihydro-5*H*-benzo[*b*][1,4]thiazepin-4-one (B12). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.728−1.749 (m, 4H), 1.443−1.580 (m, 2H), 1.613−1.749 (m, 4H), 2.588(s, 3H), 2.625−2.771 (m, 1H), 2.735 (t, 2H, J = 7.2 Hz), 3.621 (t, 2H, J = 6.9 Hz), 4.374 (d, 2H, J = 5.7 Hz), 6.369 (s, 1H), 6.734−6.800 (m, 3H), 7.187 (t, 1H, J = 7.8 Hz), 7.571 (s, 1H), 8.342 (s, 1H).



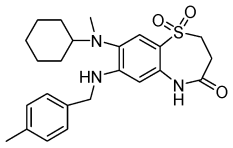
compound **B12**

8-(Cyclohexyl-methyl-amino)-7-[(5-methyl-thiophen-2-ylmethyl)-amino]-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo-[*b*][1,4]thiazepin-4-one (B13). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.008−1.252 (m, 4H), 1.443−1.596 (m, 2H), 1.653−1.775 (m, 4H), 2.449(s, 3H), 2.605 (s, 3H), 2.624−2.770 (m, 1H), 2.757 (t, 2H, J = 7.2 Hz), 3.714 (t, 2H, J = 6.9 Hz), 4.476 (brs, 2H), 6.286 (s, 1H), 6.612 (d, 1H, J = 2.7 Hz), 6.770 (d, 1H, J = 2.7 Hz), 7.541 (s, 1H), 7.585 (s, 1H).



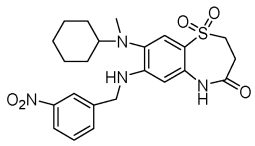
compound **B13**

8-(Cyclohexyl-methyl-amino)-7-(4-methyl-benzylamino)-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B14). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.239−1.319 (m, 4H), 1.453−1.680 (m, 2H), 1.633−1.859 (m, 4H), 2.435 (s, 3H), 2.694 (s, 3H), 2.625−2.771 (m, 1H), 2.824 (t, 2H, J = 7.2 Hz), 3.774 (t, 2H, J = 6.9 Hz), 4.429 (brs, 2H), 6.275 (s, 1H), 7.340 (brs, 4H), 7.668 (s, 1H).



compound **B14**

8-(Cyclohexyl-methyl-amino)-7-(3-nitro-benzylamino)-1,1-dioxo-1,2,3,5-tetrahydro-1λ^6-benzo[*b*][1,4]thiazepin-4-one (B15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.128−1.499 (m, 4H), 1.443−1.606 (m, 2H), 1.613−1.813 (m, 4H), 2.588 (s, 3H), 2.658−2.771 (m, 1H), 2.732 (t, 2H, J = 7.2 Hz), 3.711 (t, 2H, J = 6.9 Hz), 4.543 (brs, 2H), 6.140 (s, 1H), 7.559 (t, 1H, J = 7.8 Hz), 7.642−7.798 (m, 3H), 8.194 (s, 1H), 8.188 (s, 1H).

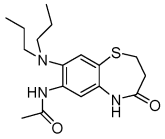


compound **B15**

Method 2. The corresponding acylating reagent (anhydride, isocyanate, or isothiocyanate; 0.12 mmol) was added to a solution of 0.10 mmol of **I** or **II** in 5 mL of anhydrous DCM. The reaction mixture was stirred mechanically on an

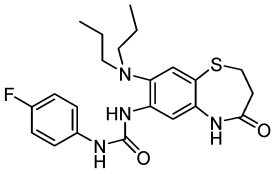
H + P Labortechnik GmbH parallel synthesizer at 45 °C for at least 12 h. The solvent then was evaporated in vacuum to obtain the crude product. The final products were characterized after chromatography purification on silica gel. The yields range from 70 to 90%.

***N*-(8-Dipropylamino-4-oxo-2,3,4,5-tetrahydro-benzo[*b*]-[1,4]thiazepin-7-yl)-acetamide (A6).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.820 (t, 6H, J = 7.2 Hz),1.283−1.358 (m, 4H), 2.117 (s, 3H), 2.404 (t, 2H, J = 6.9 Hz), 2.759−2.808 (m, 4H), 3.322 (t, 2H, J = 6.9 Hz), 7.339 (s, 1H), 7.987 (s, 1H), 8.971 (s, 1H), 9.715 (s, 1H).



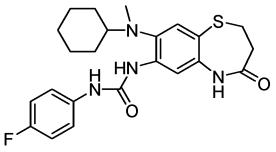
compound **A6**

1-(8-Dipropylamino-4-oxo-2,3,4,5-tetrahydro-benzo[*b*]-[1,4]thiazepin-7-yl)-3-(4-fluoro-phenyl)-urea (A7). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.805 (t, 6H, J = 7.5 Hz),1.308−1.333 (m, 4H), 2.425 (t, 2H, J = 6.9 Hz), 2.807−2.858 (m, 4H), 3.324 (t, 2H, J = 6.9 Hz), 7.132 (m, 2H), 7.325 (s, 1H), 7.478 (m, 2H), 8.033 (s, 1H), 8.575 (s, 1H), 9.678 (s, 1H), 9.702 (s, 1H).



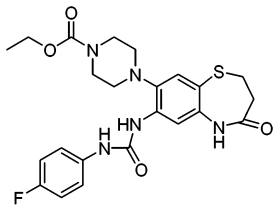
compound **A7**

1-[8-(Cyclohexyl-methyl-amino)-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-7-yl]-3-(4-fluoro-phenyl)-urea (A13). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.094−1.224 (m, 6H), 1.690−1.892 (m, 4H), 2.426 (t, 2H, J = 6.9 Hz), 2.592 (s, 3H), 2.592−2.601 (m, 1H), 3.352 (t, 2H, J = 6.9 Hz), 7.107−7.165 (m, 2H), 7.316 (s, 1H), 7.463−7.508 (m, 2H), 7.993 (s, 1H), 8.465 (s, 1H), 9.669 (s, 1H), 9.695 (s, 1H).



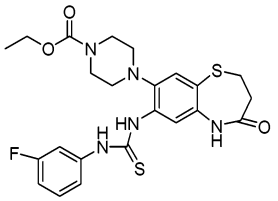
compound **A13**

4-{7-[3-(4-Fluoro-phenyl)-ureido]-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-8-yl}-piperazine-1-carboxylic Acid Ethyl Ester (A17). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.212 (t, 3H, J = 7.2 Hz), 2.422 (t, 2H, J = 6.9 Hz), 2.780 (brs, 4H), 3.323 (t, 2H, J = 6.9 Hz), 3.616 (brs, 4H), 4.096 (q, 2H, J = 7.2 Hz), 7.122−7.181 (m, 2H), 7.283 (s, 1H), 7.468−7.514 (m, 2H), 7.975 (s, 1H), 8.223 (s, 1H), 9.617 (s, 1H), 9.710 (s, 1H).



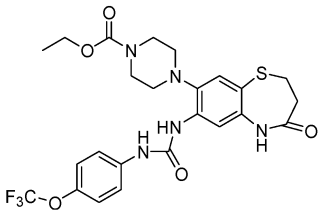
compound **A17**

4-{7-[3-(3-Fluoro-phenyl)-thioureido]-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-8-yl}-piperazine-1-carboxylic Acid Ethyl Ester (A18). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.193 (t, 3H, J = 7.2 Hz), 2.427 (t, 2H, J = 6.9 Hz), 2.788 (brs, 4H), 3.381 (t, 2H, J = 6.9 Hz), 3.428 (brs, 4H), 4.056 (q, 2H, J = 7.2 Hz), 6.980−7.042 (m, 1H), 7.250 (s, 1H), 7.277−7.306 (m, 1H), 7.371−7.421 (m, 1H), 7.616−7.660 (m, 1H), 7.915 (s, 1H), 9.346 (s, 1H), 9.752 (s, 1H), 10.325 (s, 1H).



compound **A18**

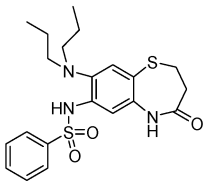
4-{4-Oxo-7-[3-(4-trifluoromethoxy-phenyl)-ureido]-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-8-yl}-piperazine-1-carboxylic Acid Ethyl Ester (A19). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.185(t, 3H, J = 7.2 Hz), 2.389 (t, 2H, J = 6.9 Hz), 2.770 (brs, 4H), 3.323 (t, 2H, J = 6.9 Hz), 3.685 (brs, 4H), 4.082 (q, 2H, J = 7.2 Hz), 7.279 (s, 1H), 7.310 (d, 2H, J = 8.4 Hz), 7.593 (d, 2H, J = 8.4 Hz) 7.959 (s, 1H), 8.273 (s, 1H), 9.717 (s, 1H), 9.794 (s, 1H).



compound **A19**

Method 3. A mixture of 0.3 mmol of pyridine and 0.12 mmol of sulfonyl chloride was added to a solution of 0.10 mmol of **I** or **II** in 5 mL of dry DCM. After the reaction mixture was stirred at 45 °C for more than 5 h, the solvent was evaporated in vacuum. The final products were characterized after chromatography purification on silica gel. For a typical compound, for example, **A8**, 33 mg of white powder was obtained in 76% yield with an HPLC purity of >99%.

***N*-(8-Dipropylamino-4-oxo-2,3,4,5-tetrahydro-benzo[*b*]-[1,4]thiazepin-7-yl) -benzene Sulfonamide (A8).** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.777 (t, 6H, J = 7.2 Hz),1.249−1.252 (m, 4H), 2.576 (t, 2H, J = 6.9 Hz), 2.687−2.820 (m, 4H), 3.397 (t, 2H, J = 6.9 Hz), 7.287 (s, 1H), 7.356 (s, 1H), 7.456−7.575 (m, 3H), 7.723−7.882 (m, 2H), 8.385 (brs, 1H).



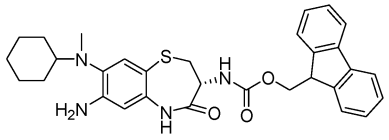
compound **A8**

L-*N*-(Fluorenylmethyloxycarbonyl)-cysteine. Triethylsilane (7 mL, 40 mmol) and TFA (3 mL, 40 mmol) were added at room temperature to a solution of L-Fmoc-Cys-(Trt)-OH (5.0 g, 8 mmol) in 50 mL of DCM. After 60 min, the mixture was concentrated in vacuo to afford a yellow oil. The product was purified using silica gel column chromatography, eluting with ethyl acetate/petroleum ether, and 1.54 g of a white solid was obtained. Yield: 90%

General Procedure for the Synthesis of Intermediates 10 and 11. A solution of 1.0 equiv of L-Fmoc-Cys(Trt)-OH in 50 mL of THF was added dropwise to a magnetically stirred solution of 1.0 equiv (typically 5.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene and 2.0 equiv of DIPEA in 50 mL of THF. The reaction mixture was continuously stirred for an additional 1 h at room temperature until DFDNB completely converted to **9**; the reaction was monitored by LC-MS analysis. Then the amine was added for additional 2 h at room temperature. The reaction mixture was evaporated in vacuo to dryness, and **10** was obtained as a yellow solid. For a typical compound, for example, 3-(5-dipropylamino-2,4-dinitro-phenylsulfanyl)-2-(9*H*-fluoren-9- ylmethoxycarbonylamino)-propionic acid, 2.923 g of yellow powder was obtained in 96% yield with an HPLC purity of >99%. ESI-MS: *m*/*z* 609.1 $(M + H)^+$. The procedure for the synthesis of **11** was similar to that of **6**. For a typical compound, for example, 3-(5-dipropylamino-2,4-dinitrobenzenesulfonyl)-2-(9*H*- fluoren-9-ylmethoxycarbonylamino)-propionic acid, 1.824 g of yellow powder was obtained in 95% yield with an HPLC purity of >99%. ESI-MS: *m*/*z* 641.1 $(M + H)^+$.

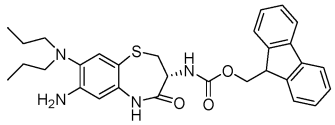
General Procedure for the Synthesis of III and IV. Compound **10** or **11** (5 mmol) in 50 mL of ethanol was completely reduced by adding it to a mixture of $SnCl_2 \cdot 2H_2O$ (30 mmol) under reflux for 8 h until the completion, which was monitored by a fast LC-MS system. The resulting mixture was concentrated under reduced pressure to give crude compound **12** or **13**. Compound **12** or **13** was dissolved in 40 mL THF/H_2O (1:1, v/v), and EDC·HCl (15 mmol) was added; the mixture was allowed to react for 3 h until the 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 purified by silica gel column chromatography, eluting with ethyl acetate/petroleum ether. For a typical compound, for example, **C1**, 1.629 g of pale powder was obtained in 60% yield with an HPLC purity of >99%.

[7-Amino-8-(cyclohexyl-methyl-amino)-4-oxo-2,3,4,5-tetrahydro-benzo [*b*][1,4]thiazepin-3-yl]-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (C1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.038−1.163 (m, 4H), 1.229−1.345 (m, 2H), 1.680−1.703 (m, 4H), 2.512 (s, 3H), 2.643−2.695 (m, 1H), 2.932 (t, 1H, J = 11.6 Hz), 3.406−3.435 (m, 1H), 4.075−4.145 (m,1H), 4.164−4.236 (m, 3H), 5.162 (brs, 2H), 6.447 (s, 1H), 7.038 (s, 1H), 7.312 (d, 2H, J = 7.2 Hz), 7.400 (t, 2H, J = 7.2 Hz), 7.683 (t, 2H, J = 7.2 Hz), 7.755 (d, 1H, J = 8.8 Hz), 7.874 (d, 2H, J = 7.2 Hz), 9.720 (s, 1H).



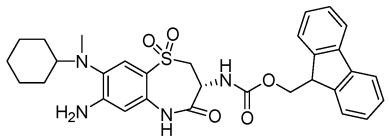
compound **C1**

(7-Amino-8-dipropylamino-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4] thiazepin-3-yl)-carbamic Acid 9*H*-fluren-9-ylmethyl Ester (C4). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.818 (t, 6H, J = 7.2 Hz), 1.290−1.313 (m, 4H), 2.750 (t, 4H, J = 7.2 Hz), 2.930 (t, 1H, J = 11.6 Hz), 3.406−3.452 (m, 1H), 4.090−4.120 (m,1H), 4.180−4.238 (m, 3H), 5.230 (brs, 2H), 6.445 (s, 1H), 7.065 (s, 1H), 7.312 (d, 2H, J = 7.2 Hz), 7.401 (t, 2H, J = 7.2 Hz), 7.683 (t, 2H, J = 7.2 Hz), 7.753 (d, 1H, J = 8.4 Hz), 7.874 (d, 2H, J = 7.2 Hz), 9.731 (s, 1H).



compound **C4**

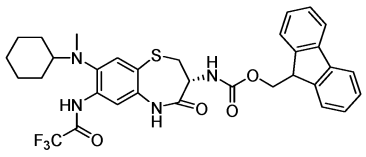
[7-Amino-8-(cyclohexyl-methyl-amino)-1,1,4-trioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo[*b*][1,4]thiazepin-3-yl]-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (D1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.048−1.171 (m, 4H), 1.209−1.346 (m, 2H), 1.680−1.721 (m, 4H), 2.536 (s, 3H), 2.639−2.693 (m, 1H), 3.597 (t, 1H, J = 11.6 Hz), 3.943−4.038 (m, 1H), 4.187−4.362 (m, 4H), 5.919 (brs, 2H), 6.453 (s, 1H), 7.288 (s, 1H), 7.312 (d, 2H, J = 7.2 Hz), 7.406 (t, 2H, J = 7.2 Hz), 7.680 (t, 2H, J = 7.2 Hz), 7.766 (d, 1H, J = 8.8 Hz), 7.880 (d, 2H, J = 7.2 Hz), 10.087 (s, 1H).



compound **D1**

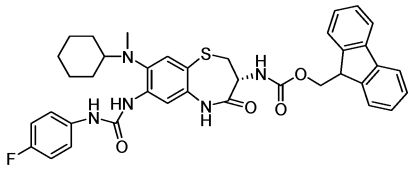
The procedures for the synthesis of **14** and **15** are similar to that of **A13**.

[8-(Cyclohexyl-methyl-amino)-4-oxo-7-(2,2,2-trifluoro-acetylamino)-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-3-yl]-carbamic Acid 9*H*-Fluoren-9- ylmethyl Ester (C2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.000−1.194 (m, 4H), 1.224−1.352 (m, 2H), 1.537−1.668 (m, 4H), 2.602 (s, 3H), 2.663−2.718 (m, 1H), 3.104 (t, 1H, J = 11.6 Hz), 3.538−3.583 (m, 1H), 4.120−4.278 (m, 4H), 7.312 (d, 2H, J = 7.2 Hz), 7.400 (s, 1H), 7.400 (t, 2H, J = 7.2 Hz), 7.512 (s, 1H), 7.680 (t, 2H, J = 7.2 Hz), 7.840 (d, 1H, J = 8.8 Hz), 7.874 (d, 2H, J = 7.2 Hz), 10.019 (s, 1H), 10.396 (s, 1H).



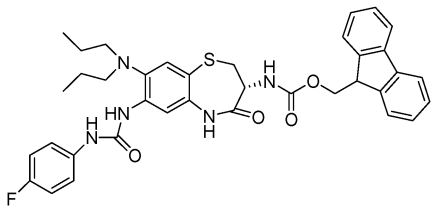
compound **C2**

{**8-(Cyclohexyl-methyl-amino)-7-[3-(4-fluoro-phenyl)-ureido]-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-3-yl**}**-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (C3).** ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.027−1.225 (m, 4H), 1.224−1.352 (m, 2H), 1.808−1.887 (m, 4H), 2.593 (s, 3H), 2.636−2.655 (m, 1H), 3.040 (t, 1H, J = 11.6 Hz), 3.491−3.536 (m, 1H), 4.125−4.255 (m, 4H), 7.123 (t, 2H, J = 8.8 Hz), 7.311 (t, 2H, J = 7.2 Hz), 7.354 (s, 1H), 7.399 (t, 2H, J = 7.2 Hz), 7.461−7.495 (m, 2H), 7.682 (t, 2H, J = 7.2 Hz), 7.807 (d, 1H, J = 8.8 Hz), 7.872 (d, 2H, J = 7.2 Hz), 8.046 (s, 1H), 8.485 (s, 1H), 9.678 (s, 1H), 9.966 (s, 1H).



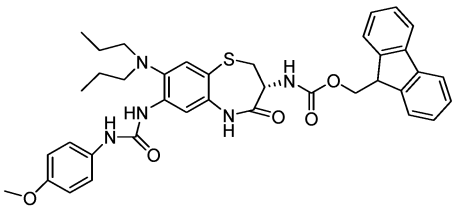
compound **C3**

{**8-Dipropylamino-7-[3-(4-fluoro-phenyl)-ureido]-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-3-yl**}**-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (C5).** ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.793 (t, 6H, J = 7.4 Hz), 1.272−1.349 (m, 4H), 2.830 (t, 4H, J = 7.6 Hz), 3.040 (t, 1H, J = 11.6 Hz), 3.489−3.534 (m, 1H), 4.169−4.261 (m, 4H), 7.123 (t, 2H, J = 8.8 Hz), 7.311 (t, 2H, J = 7.6 Hz), 7.354 (s, 1H), 7.399 (t, 2H, J = 7.6 Hz), 7.461−7.495 (m, 2H), 7.682 (t, 2H, J = 8.0 Hz), 7.803 (d, 1H, J = 8.4 Hz), 7.872 (d, 2H, J = 7.6 Hz), 8.046 (s, 1H), 8.485 (s, 1H), 9.678 (s, 1H), 9.966 (s, 1H).



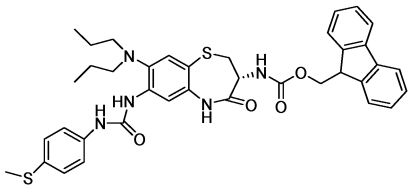
compound **C5**

{**8-Dipropylamino-7-[3-(4-methoxy-phenyl)-ureido]-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-3-yl**}**-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (C6).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.679 (t, 6H, J = 7.0 Hz),1.123−1.167 (m, 4H), 2.581 (t, 4H, J = 7.0 Hz), 2.985 (t, 1H, J = 11.5 Hz), 3.846 (s, 3H), 3.918−3.953 (m, 1H), 4.181 (t,1H, J = 7.0 Hz), 4.309−4.369 (m, 2H), 4.599−4.649 (m, 1H), 5.997 (d, 1H, J = 6.5 Hz), 6.957 (d, 2H, J = 9.0 Hz), 7.301 (t, 2H, J = 7.6 Hz), 7.296 (s, 1H), 7.283 (t, 2H, J = 7.6 Hz), 7.385 (t, 2H, J = 7.6 Hz), 7.572 (t, 2H, J = 7.6 Hz), 7.747 (d, 2H, J = 7.6 Hz), 8.154 (s, 1H), 8.271 (s, 1H), 8.382 (s, 1H).



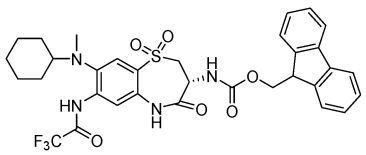
compound **C6**

{**8-Dipropylamino-7-[3-(4-methylsulfany-phenyl)-ureido]-4-oxo-2,3,4,5- tetrahydro-benzo[*b*][1,4]thiazepin-3-yl**}**-carbamic Acid 9*H*-Fluren-9-ylmethyl Ester (C8).** ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.794 (t, 6H, J = 8.4 Hz), 1.271−1.352 (m, 4H), 2.422 (s, 3H), 2.831 (t, 4H, J = 8.4 Hz), 2.831 (t, 1H, J = 11.6 Hz), 3.490−3.535 (m, 1H), 4.133−4.264 (m, 4H), 7.210 (d, 2H, J = 8.4 Hz), 7.312 (t, 2H, J = 7.6 Hz), 7.359 (s, 1H), 7.412 (t, 2H, J = 7.6 Hz), 7.441 (t, 2H, J = 8.4 Hz), 7.683 (t, 2H, J = 8.4 Hz), 7.803 (d, 1H, J = 8.4 Hz), 7.873 (d, 2H, J = 7.6 Hz), 8.092 (s,1H), 8.601 (s, 1H), 9.662 (s, 1H), 9.964 (s, 1H).



compound **C8**

[8-(Cyclohexyl-methyl-amino)-1,1,4-trioxo-7-(2,2,2-trifluoro-acetylamino)-2,3,4,5-tetrahydro-1H-1λ^6-benzo[*b*]-[1,4]thiazepin-3-yl]-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (D4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.091−1.376 (m, 4H), 1.583−1.657 (m, 2H), 1.792−1.852 (m, 4H), 2.657 (m, 1H), 2.716 (s, 3H), 3.594 (t, 1H, J = 11.6 Hz), 4.174−4.203 (m, 1H), 4.230−4.271 (m, 1H), 4.358−4.393 (d, 2H, J = 6.5 Hz), 4.675−4.725 (m, 1H), 6.044 (d, 1H, J = 6.5 Hz), 7.300−7.333 (m, 2H), 7.407 (t, 2H, J = 7.2 Hz), 7.549−7.571 (m, 2H,), 7.563 (d, 2H, J = 8.0 Hz), 7.871 (s, 1H), 7.908 (s, 1H), 8.325 (s, 1H), 9.850 (s, 1H).



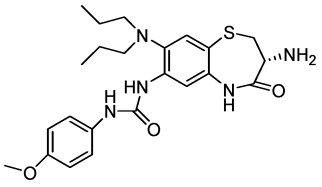
compound **D4**

General Procedure for the Synthesis of 16 and 17. Method 1. A solution of **14** (1 mmol) or **15** (1 mmol) in 2 mL of piperidine was stirred at room temperature for 30 min. The resulting mixture was evaporated in vacuum and further purified by silica gel column chromatography, eluting with ethyl acetate/petroleum ether.

Method 2.[12] Peperazine (15 mmol) was dissolved in 10 mL of anhydrous DCM, and chloromethylated resin [4.19 mequiv of Cl per g of resin, 1% divinylbenzene (DVB)] (5 mmol) was added. After it was stirred overnight at room temperature, the resin was washed with DMF (3×), MeOH (3×), and DCM (3×) and then dried in vacuo.

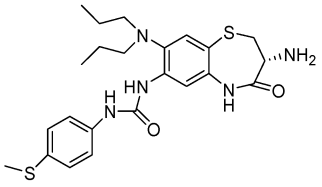
The suspension of 10 equiv of polymer **18** in a DCM solution (10 mL) of **14** or **15** and stirring for 72 h lead to the resulting amine being obtained after simple filtration of the polymer and evaporation of the solvent. All dibenzofulvene liberated was scavenged by the insoluble polymer.

1-(3-Amino-8-dipropylamino-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-7-yl)-3-(4-methoxy-phenyl)-urea (C7). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.790 (t, 6H, J = 7.6 Hz), 1.271−1.336 (m, 4H), 2.746 (t, 1H, J = 11.6 Hz), 2.812 (t, 4H, J = 7.6 Hz), 3.330−3.374 (m, 1H), 3.404−3.446 (m, 1H), 3.708 (s, 3H), 6.868 (d, 2H, J = 8.8 Hz), 7.316 (s, 1H), 7.364 (d, 2H, J = 8.8 Hz), 8.042 (s,1H), 8.494 (s, 1H), 9.438 (s, 1H), 9.856 (s, 1H).



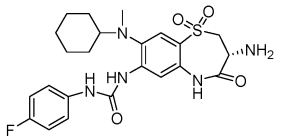
compound **C7**

1-(3-Amino-8-dipropylamino-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4] thiazepin-7-yl)-3-(4-methylsulfanyl-phenyl)-urea (C9). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.790 (t, 6H, J = 7.2 Hz), 1.220−1.347 (m, 4H), 2.427 (s, 3H), 2.826 (t, 4H, J = 8.0 Hz), 2.845−2.874 (m, 1H), 3.502−3.548 (m,2H), 5.400 (brs, 2H), 7.215 (d, 2H, J = 8.8 Hz), 7.345 (s, 1H), 7.446 (d, 2H, J = 8.8 Hz), 8.073 (s, 1H), 8.623 (s, 1H), 9.758 (s, 1H), 10.060 (s, 1H).



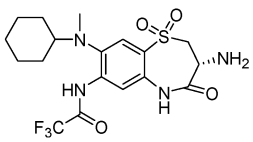
compound **C9**

1-[3-Amino-8-(cyclohexyl-methyl-amino)-1,1,4-trioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo[*b*][1,4]thiazepin-7-yl]-3-(4-fluoro-phenyl)-urea (D2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.965−1.106 (m, 4H), 1.524−1.567 (m, 2H), 1.821−1.871 (m, 4H), 2.427 (s, 3H), 2.454−2.476 (m, 1H), 3.555−3.622 (m, 1H), 3.950−4.016 (m, 2H), 7.149−7.182 (t, 2H, J = 8.0 Hz), 7.342−7.367 (m, 2H), 7.681 (s, 1H), 8.464 (s, 1H), 8.538 (s, 1H), 8.651 (s, 1H), 11.031 (s, 1H).



compound **D2**

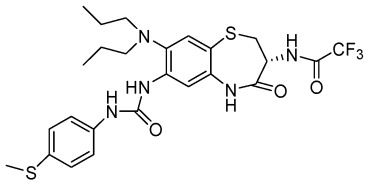
***N*-[3-Amino-8-(cyclohexyl-methyl-amino)-1,1,4-trioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo[*b*][1,4]thiazepin-7-yl]-2,2,2-trifluoro-acetamide (D5).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.215−1.330 (m, 4H), 1.623−1.648 (m, 2H), 1.765−1.870 (m, 4H), 2.546−2.661 (m, 1H), 2.685 (s, 3H), 3.607 (t, 1H, J = 12.0 Hz), 3.836−3.873 (m, 1H), 3.926−3.966 (m, 1H), 7.857 (s, 1H), 8.243 (s, 1H), 8.307 (s, 1H), 9.842 (s, 1H).



compound **D5**

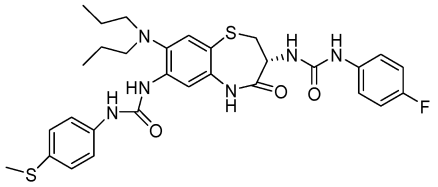
Derivatization of 16 and 17 at 3-Amino Group. The procedure for the derivatization of **16** and **17** at the 3-amino group was similar to that of **A**. All the reactions took place at room temperature.

***N*-{8-Dipropylamino-7-[3-(4-methylsulfanyl-phenyl)-ureido]-4-oxo- 2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-3-yl}-2,2,2-trifluoro-acetamide (C10).** ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.798 (t, 6H, J = 7.2 Hz), 1.224−1.343 (m, 4H), 2.431 (s, 3H), 2.838 (t, 4H, J = 7.2 Hz), 3.242 (t, 1H, J = 12.0 Hz), 3.574−3.619 (m, 1H), 4.369−4.399 (m, 1H), 7.225 (d, 2H, J = 8.8 Hz), 7.372 (s, 1H), 7.450 (d, 2H, J = 8.8 Hz), 8.117 (s, 1H), 8.630 (s, 1H), 9.725 (s, 1H), 9.874 (d, 1H, J = 7.2 Hz), 10.116 (s, 1H).



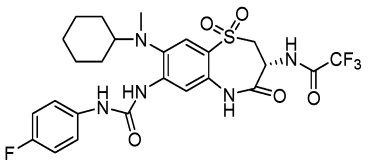
compound **C10**

1-{8-Dipropylamino-7-[3-(4-methylsulfanyl-phenyl)-ureido]-4-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]thiazepin-3-yl}-3-(4-fluoro-phenyl)-urea (C11). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.811 (t, 6H, J = 7.2 Hz), 1.285−1.378 (m, 4H), 2.429 (s, 3H), 2.849 (t, 4H, J = 8.0 Hz), 2.953 (t, 1H, J = 11.6 Hz), 3.579−3.623 (m, 1H), 4.324−4.390 (m, 1H), 6.635 (d, 1H, J = 8.8 Hz), 7.001−7.045 (m, 2H), 7.223 (d, 2H, J = 8.8 Hz), 7.249−7.329 (m, 2H), 7.393 (s, 1H), 7.442 (d, 2H, J = 8.8 Hz), 8.096 (s, 1H), 8.603 (s, 1H), 8.832 (s, 1H), 9.668 (s, 1H), 10.135 (s, 1H).



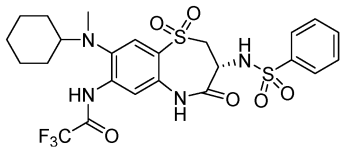
compound **C11**

***N*-{8-(Cyclohexyl-methyl-amino)-7-[3-(4-fluoro-phenyl)-ureido]-1,1,4-trioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo-[*b*][1,4]thiazepin-3-yl}-2,2,2-trifluoro-acetamide (D3).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.938−1.106 (m, 4H), 1.529−1.597 (m, 2H), 1.821−1.871 (m, 4H), 2.471 (s, 3H), 2.454−2.476 (m, 1H), 3.624 (t, 1H, J = 12.0 Hz), 4.410−4.451 (m, 1H), 4.905−4.952 (m, 1H), 7.183−7.212 (m, 2H), 7.369−7.395 (m, 2H), 7.705 (d, 1H, J = 6.0 Hz), 7.725 (s, 1H), 8.177 (s, 1H), 8.515 (s, 1H), 8.670 (s, 1H), 11.343 (s, 1H).



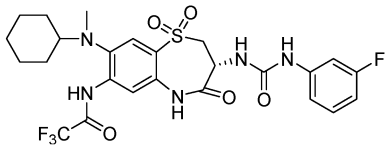
compound **D3**

***N*-[3-Benzenesulfonylamino-8-(cyclohexyl-methyl-amino)-1,1,4-trioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo[*b*][1,4]-thiazepin-7-yl]-2,2,2-trifluoro- acetamide (D6).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.295−1.402 (m, 4H), 1.642−1.667 (m, 2H), 1.792−1.830 (m, 4H), 2.650−2.693 (m, 1H), 2.733 (s, 3H), 3.694 (t, 1H, J = 12.0 Hz), 3.986−4.028 (m, 1H), 4.326−4.379 (m, 1H), 6.142 (d, 1H, J = 8.5 Hz), 7.494 (t, 2H, J = 7.5 Hz), 7.604 (t, 1H, J = 7.5 Hz), 7.742 (d, 2H, J = 7.5 Hz), 7.849 (s, 1H), 8.118 (s, 1H), 8.181 (s, 1H), 9.856 (s, 1H).



compound **D6**

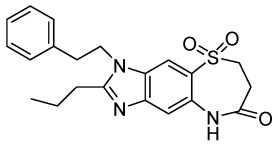
***N*-{8-(Cyclohexyl-methyl-amino)-3-[3-(3-fluoro-phenyl)-ureido]-1,1,4-trioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzo-[*b*][1,4]thiazepin-7-yl}-2,2,2-trifluoro-acetamide (D7).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.227−1.329 (m, 4H), 1.628−1.655 (m, 2H), 1.778−1.799 (m, 4H), 2.643−2.685 (m, 1H), 2.718 (s, 3H), 3.691 (t, 1H, J = 12.0 Hz), 3.986−4.016 (m, 1H), 4.325−4.390 (m, 1H), 6.992−7.064 (m, 3H), 7.292−7.336 (m, 1H), 7.452 (d, 1H, J = 6.0 Hz), 7.873 (s, 1H), 8.360 (s, 2H), 8.693 (s, 1H), 9.855 (s, 1H).



compound **D7**

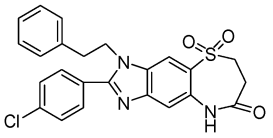
General Procedure for the Synthesis of E. A solution of **II** (0.1 mmol) in 5 mL of anhydrous DCM was added to a mixture of aldehyde (0.2 mmol) and glacetic acid (100 μL) at room temperature under mechanical shaking. The chemical conversion was monitored by LC-MS analysis. After the reaction was completed, the solution was evaporated under reduced pressure to dryness. The crude residue was dissolved in 15 mL of DCM and washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL). After it was completely dried over anhydrous Na_2SO_4, the filtrate was concentrated in vacuo to obtain **E**. The final products were characterized after chromatography purification on silica gel. For a typical compound, for example, **E1**, 24 mg of white powder was obtained in 60% yield with an HPLC purity >99%.

5,5-Dioxo-3-phenethyl-2-propyl-5,6,7,9-tetrahydro-3*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]inden-8-one (E1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.879 (t, 3H, J = 7.5 Hz), 1.629−1.703 (m, 2H), 2.502−2.547 (m, 4H), 3.008 (t, 2H, J = 6.6 Hz), 3.772 (t, 2H, J = 6.9 Hz), 4.529 (t, 2H, J = 6.6 Hz), 7.977−7.008 (m, 2H), 7.156−7.191 (m, 3H), 7.308 (s, 1H), 7.866 (s, 1H), 10.022 (s, 1H).



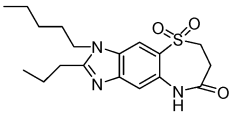
compound **E1**

2-(4-Hydroxy-phenyl)-5,5-dioxo-3-phenethyl-5,6,7,9-tetrahydro-3*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]inden-8-one (E2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.560 (t, 2H, J = 6.9 Hz), 2.913 (t, 2H, J = 6.6 Hz), 3.821 (t, 2H, J = 6.9 Hz), 4.663 (t, 2H, J = 6.6 Hz), 6.777−6.808 (m, 2H), 7.073−7.096 (m, 3H), 7.434 (s, 1H), 7.574 (s, 4H), 8.075 (s, 1H), 10.111 (s, 1H).



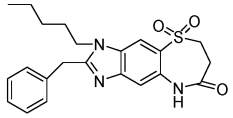
compound **E2**

5,5-Dioxo-3-pentyl-2-propyl-5,6,7,9-tetrahydro-3*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]inden-8-one (E3). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.916 (t, 3H, J = 6.9 Hz), 1.075 (t, 3H, J = 6.9 Hz), 1.296−1.387 (m, 4H), 1.785−1.836 (m, 2H), 1.910−2.038 (m, 2H), 2.745 (t, 2H, J = 7.2 Hz), 2.877 (t, 2H, J = 7.5 Hz), 3.790 (t, 2H, J = 7.2 Hz), 4.153 (t, 2H, J = 7.5 Hz), 7.518 (s, 1H), 8.025 (s, 1H), 8.100 (s, 1H).



compound **E3**

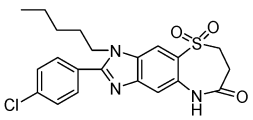
2-Benzyl-5,5-dioxo-3-pentyl-5,6,7,9-tetrahydro-3*H*- 5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]-inden-8-one (E4). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.778 (t, 3H, J = 6.9 Hz), 1.190−1.234 (m, 4H), 1.419−1.441 (m, 2H), 2.570 (t, 2H, J = 7.2 Hz), 3.816 (t, 2H, J = 7.2 Hz), 4.263 (t, 2H, J = 7.5 Hz), 4.372 (s, 2H), 7.295−7.330 (m, 5H), 7.396 (s, 1H), 8.032 (s, 1H), 10.081 (s, 1H).



compound **E4**

2-(4-Chloro-phenyl)-5,5-dioxo-3-pentyl-5,6,7,9-tetrahydro-3*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]inden-8-one (E5). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.749 (t, 3H, J = 7.2 Hz), 1.123−1.174 (m, 4H), 1.643−1.686 (m, 2H), 2.576 (t, 2H, J = 7.2 Hz), 3.863 (t, 2H, J = 7.2 Hz), 4.407 (t, 2H, J

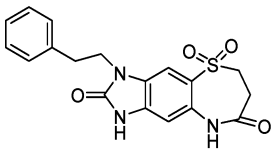
= 7.2 Hz), 7.493 (s, 1H), 7.695 (d, 2H, J = 8.1 Hz), 7.842 (d, 2H, J = 8.1 Hz), 8.200 (s, 1H), 10.151 (s, 1H).



compound **E5**

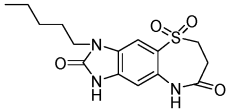
General Procedure for the Synthesis of F and G. A solution of triphosgene (0.1 mmol) or carbon disulfide (0.2 mmol) in DCM (1 mL) was added dropwise at room temperature to a stirred solution of **II** (0.1 mmol) in anhydrous DCM (5 mL) and Et_3N (0.1 mmol). The reaction was monitored by LC-MS analysis until that the reaction was completed. The solution was diluted with 2 mL of water and extracted with DCM (2 × 10 mL). The organic layers were combined, successively washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo. The residue was finally purified on silica gel to obtain the pure **F** and **G**. For a typical compound, for example, **F1**, 24 mg of pale powder was obtained in 65% yield with an HPLC purity of >99%.

5,5-Dioxo-3-phenethyl-5,6,7,9-tetrahydro-1*H*,3*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]indene-2,8-dione (F1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.513 (t, 2H, J = 7.2 Hz), 2.927 (t, 2H, J = 6.9 Hz), 3.751 (t, 2H, J = 7.2 Hz), 4.081 (t, 2H, J = 6.9 Hz), 6.741 (s, 1H), 7.148−7.241 (m, 5H), 7.305 (s, 1H), 9.956 (s, 1H), 11.383 (s, 1H).



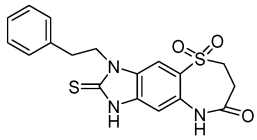
compound **F1**

5,5-Dioxo-3-pentyl-5,6,7,9-tetrahydro-1*H*,3*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]-indene-2,8-dione (F2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.843 (t, 3H, J = 6.9 Hz), 1.223−1.319 (m, 4H), 1.599−1.645 (m, 2H), 2.561 (t, 2H, J = 7.2 Hz), 3.779−3.849 (m, 4H), 6.779 (s, 1H), 7.498 (s, 1H), 9.996 (s, 1H), 11.403 (s, 1H).



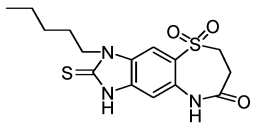
compound **F2**

5,5-Dioxo-3-phenethyl-2-thioxo-2,3,5,6,7,9-hexahydro-1*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]inden-8-one (G1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.532 (t, 2H, J = 7.2 Hz), 3.012 (t, 2H, J = 7.2 Hz), 3.761 (t, 2H, J = 7.2 Hz), 4.488 (t, 2H, J = 7.2 Hz), 6.893 (s, 1H), 7.116−7.291 (m, 5H), 7.463 (s, 1H), 10.070 (s, 1H), 13.146 (brs, 1H).



compound **G1**

5,5-Dioxo-3-pentyl-2-thioxo-2,3,5,6,7,9-hexahydro-1*H*-5λ^6-thia-1,3,9-triaza-cyclohepta[*f*]-inden-8-one (G2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.860 (t, 3H, J = 6.9 Hz), 1.223−1.341 (m, 4H), 1.672−1.719 (m, 2H), 2.583 (t, 2H, J = 7.5 Hz), 3.840 (t, 2H, J = 7.5 Hz), 4.257 (t, 2H, J = 7.5 Hz), 6.952 (s, 1H), 7.782 (s, 1H), 10.126(s, 1H), 13.138 (s, 1H).



compound **G2**

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