Parallel Solution-Phase Synthesis of 4H-Benzo[1,4]thiazin-3-one and 1,1-Dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one Derivatives from 1,5-Difluoro-2,4-dinitrobenzene

Zhanguo Wang, Yunyun Yuan, Yuyan Chen, Gangchun Sun, Xianghong Wu, Shengmei Zhang, Chunyan Han, Guanxing Wang, Li Li, and Gang Liu*

Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union of Medical College, 1 Xian Nong Tan Street, Beijing 100050, P. R. China

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This paper discusses the synthesis of privileged structures 4H-benzo[1,4]thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one derivatives in a parallel solution-phase manner using 1,5-difluoro-2,4-dinitrobenzene. Each scaffold possesses four diversity points. A cheap and efficient oxidant, urea−hydrogen peroxide (UHP), was applied for the introduction of the sulfone group. The intramolecular cyclization to 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one was achieved by microwave assistance or the use of an inorganic base.

Introduction

The goal of combinatorial chemistry is to develop diverse compounds, and it has impacted both lead generation and optimization in the past decade.[1] Privileged structures are defined as a class of skeletons or substructures that are capable of binding to multiple receptors with high affinity,[2,3] enabling the medicinal chemist to rapidly determine biologically active compounds across a wide range of therapeutic areas. We have successfully developed "scaffold-directed" methods in a parallel solution-phase manner to efficiently generate privileged benzofuzed heterocycles containing oxygen or nitrogen moieties.[4−10] For heterocycles containing sulfur moieties, 4H-benzo[1,4]thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one scaffolds were both classified as privileged structures because they are frequently found in biologically active compounds across a number of different therapeutic fields, such as anxiolytic,[11] antihypertensive,[12] antidiabetic,[13] anticataract,[14] antiarrhythmic,[15] vasodilator,[16] etc. (Figure 1). Therefore, the parallel solution-phase synthesis of 4H-benzo[1,4]thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one scaffold compounds from a commercially available material 1,5-difluoro-2,4-dinitrobenzene (DFDNB) was developed in this paper (Scheme 1).

Results and Discussion

Preparation of Key Intermediates 3 and 7. The preparation of intermediates **3** and **7** are crucial for the preparation of the diverse 4H-benzo[1,4]thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one derivatives in this paper. Furthermore, when the R1 or R2 group is a hydrogen atom, **3** and **7** are the key intermediates for the construction of tricyclic scaffolds based on 4H-benzo[1,4]-thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]-thiazin-3-one, which will be discussed elsewhere. Thus, highly efficient synthesis of these compounds is important. The synthetic route is outlined in Scheme 1.

The route started from DFDNB; then, two fluorine atoms were quantitatively substituted by alkyl amines (primary amine or secondary amine) and were continuously replaced by the nucleophilic ethyl mercaptoacetate to give compound **2** in the presence of an organic base such as triethyl amine (TEA), diisopropylethylamine (DIPEA), or *N*-methylmorpholine (NMM), as described in our previously reported methods.[4,8] No unexpected side products were observed by the LC-MS analysis in these two reaction steps when exactly equivalent reactants were used. Thus, it is not necessary to further purify intermediate **2** for the next oxidation or reduction step.

Sulfone is an interesting pharmacophore displayed on many drugs. Selective oxidation of thioether to sulfone attracts great interest from organic chemists. Many methods were reported on the preparation of sulfones from sulfides. However, most of them suffer from drawbacks such as long reaction time[17] and the use of corrosive acids[18] or hazardous peracids.[19] Noble metal catalysts are often needed to promote the reaction completely for those thioether-containing electron-withdrawing groups in the adjacent oppositions. UHP,[20] an adduct of hydrogen peroxide and urea, is an inexpensive, stable, less dangerous, and facile isolating oxidant that oxidates thioether to sulfone. The byproducts of the oxidation by UHP can be washed away by water; thus, the operation is simple and safe and therefore suitable for the library synthesis.

In the present paper, we selected UHP as the oxidant to introduce a sulfone group onto **2** to produce **5** to be compatible with synthesis of the corresponding chemical library. The reaction was monitored by HPLC-MS and NMR

* To whom correspondence should be addressed. Phone: +86-10-63167165. Fax: +86-10-63167165. E-mail: gangliu27@yahoo.com.

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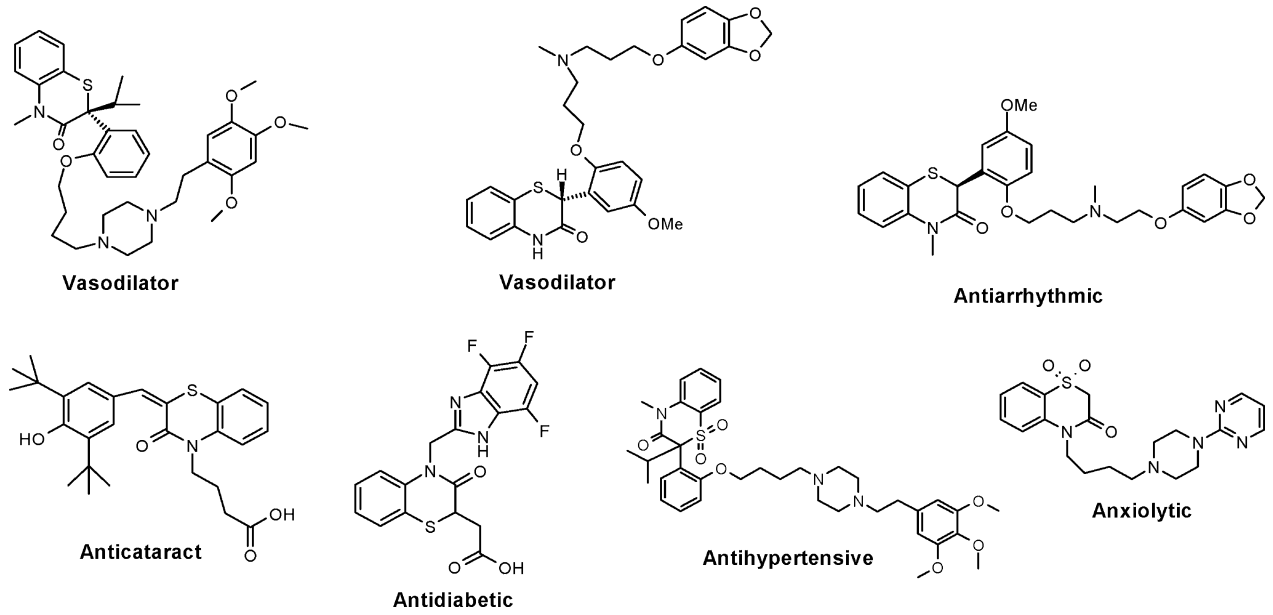
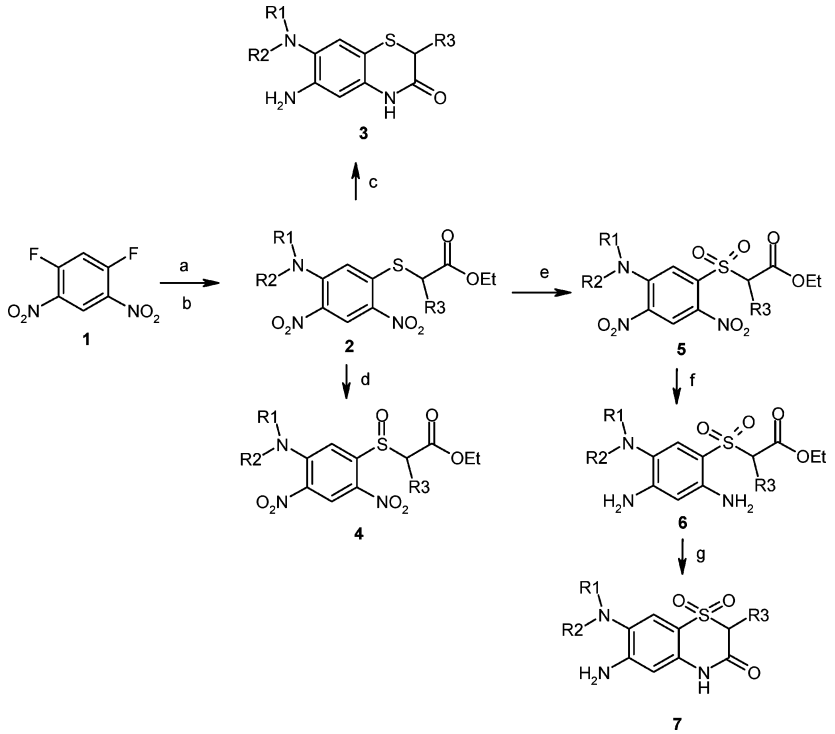


Figure 1. Representative drugs or biologically active compounds based on 4H-benzo[1,4]thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one scaffolds.

Scheme 1. Synthetic Route of 4H-Benzo[1,4]thiazin-3-one and 1,1-Dioxo-1,4-dihydro- 2H-1λ^6-benzo[1,4]thiazin-3-one Derivatives Generated from DFDNB[a]

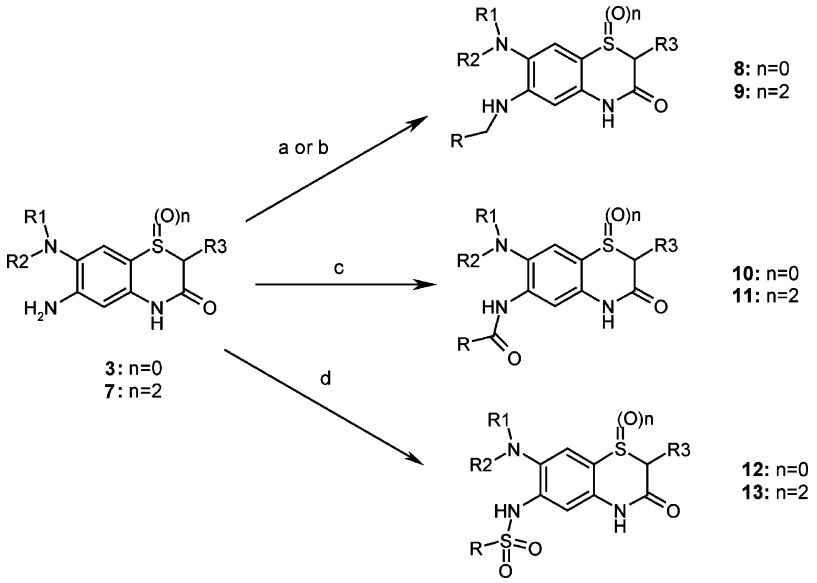


[a] (a) R_1R_2NH, DIPEA, THF, room temp; (b) $HSCH(R_3)COOCH_2CH_3$, DIPEA, THF, room temp; (c) $SnCl_2 \cdot 2H_2O$, C_2H_5OH/HCl, reflux; (d) UHP, $(CH_3CO)_2O$, CH_3CN, room temp; (e) UHP, $(CF_3CO)_2O$, CH_3CN, room temp; (f) Pd/C, $HCOONH_4$, C_2H_5OH/THF, room temp; (g) NaH, THF, reflux or microwave assistance (150 W, 80 °C).

with the oxidation of (2,4-dinitro-5-pentylamino-phenylsulfanyl)-acetic acid ethyl ester as an example. The chemical shift of methylene group of SCH_2 corresponds to a single peak at δ 3.70. However, when the sulfur atom was oxidated to sulfone, this signal was downshifted to δ 4.80 because of the electron-withdrawing effect of the sulfone group. The oxidant products **5** can only be detected by MS analysis in negative-ion mode. We also observed that the oxidation of UHP stopped at the sulfoxide stage (**4**) when $(CF_3CO)_2O$ was replaced by $(CH_3CO)_2O$. Correspondingly, the signal of these protons was split into two peaks (δ 3.72 and 4.13) because a carbon chiral center was generated. This phenomenon offers us another opportunity to synthesize sulfoxide derivatives. Further investigation and application of this new chemistry will be reported elsewhere.

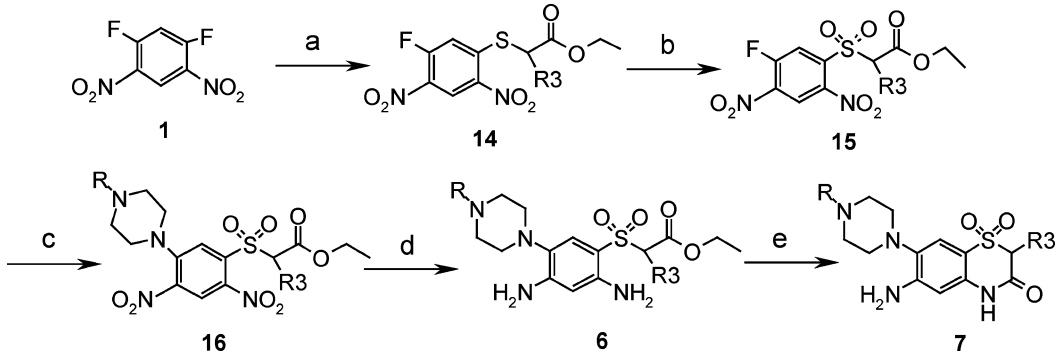
The reduction of the aromatic dinitro group was systematically studied to obtain high purity and ease of workup in the production of the corresponding chemical libraries.[4,5] Three methods were finally selected including $HCOONH_4$ with Pd/C,[4] $SnCl_2 \cdot 2H_2O$,[5] and $Na_2S_2O_4/K_2CO_3$.[5] However,

Scheme 2. Derivation of **3** and **7** at the 7-Aromatic Amino Group[a]



[a] (a) When $n = 0$, 2 molar excess $NaBH(OAc)_3$, HOAc (5%), RCHO, DCM, room temp; (b) when $n = 2$, 5 molar excess $NaBH(OAc)_3$, HOAc (5%), RCHO, DCM, room temp; (c) $(RCO)_2O$, DCM, room temp, 30 min; (d) RSO_2Cl, pyridine, DCM, microwave-assisted (100 W, 80°C, 100 psi, 60 min).

Scheme 3. Synthetic Route of Intermediate **7** Containing a Piperazinyl Group[a]

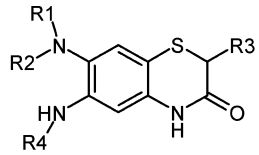


[a] (a) $HSCH(R_3)COOCH_2CH_3$, DIPEA, THF, room temp; (b) UHP, $(CH_3CO)_2O$, CH_3CN, room temp; (c) N-substituted piperizine, DIPEA, THF, room temp; (d) Pd/C, $HCOONH_4$, C_2H_5OH/THF, room temp; (e) NaH, THF, reflux or microwave assistance (150 W, 80 °C).

Pd/C could be poisoned by the sulfur atom in this study. Thus, the conversion of **2** into **3** was completed by using excess $SnCl_2 \cdot 2H_2O$ in ethanol with excellent HPLC purity and high yield detected with UV at 254 nm. It was reported that ionic liquid tetrabutylamide bromide could be used as the solvent and thus reduce the amount of $SnCl_2 \cdot 2H_2O$.[20] However, this method failed in our study. For intermediate **5** with a sulfone group, the most convenient reduction method of $HCOONH_4$ with Pd/C was chosen for the quantitative reduction of *m*-$Ar(NO_2)_2$. Compared with the synthesis of **3**, the resulting triaminobenzene **6** could not spontaneously cyclize to give compound **7**. Prolonging reaction time under increased temperature (140 °C) in DMF or 1,4-dixoane only afforded **7** in a very poor yield. We initially thought that the failure of cyclization was caused by the strong intramolecular hydrogen bonds between the adjacent amino group and the oxygen atom of sulfone. However, the addition of organic base (Et_3N) in an attemp to break such hydrogen bonds did not provide the anticipated product **7**. Interestingly, it was found that triaminobenzene **6** was very stable when exposed to the air. Considering the stability of **6**, we realized that the strong electron-withdrawing sulfone group significantly decreased the nucleophilicity of the adjacent amino group. Thus, a strong inorganic base NaH or microwave-assisted condition was finally applied that successfully gave **7** in good HPLC purity and modest yield. Microwave assistance is the optimal choice because no additional reagents are needed. We also found that the tendency toward cyclization was related to the size and order of substituted amines.

Derivation of 3 and 7 at the 7-Aromatic Amino Group. To further introduce diversity on **3** and **7**, reductive amination and acylation at the 7-NH_2 group were investigated herein as depicted in Scheme 2. The reductive amination was smoothly carried out by using a 2−5 molar excess of $NaBH(OAc)_3$. The strong electron-withdrawing property of the 4-sulfone group of **7** obviously required a larger amount of the reductive reagent. Acylation by anhydride and sulfonyl chloride adopted our reported method.[6] However, for intermediate **7** containing N-substituted piperazine, trifluoroacetylation of the 7-aromatic amino group took place as indicated by HPLC-MS analysis. Particularly, when **7** contained *N*-methyl or *N*-ethyl piperazinyl groups, trifluoroacetylation was the exclusive acylation pathway. We assumed that this was caused by adduct formation by piperazine and the trifluoroacetic anhydride of UHP. Thus, an alternative reaction approach was adopted as shown in

Table 1. Representative 4H-Benzo[1,4]thiazin-3-one Derivatives



Entry	R_1R_2N	R_3	R_4	HPLC purity (%)[a]	MS (found)	MW (calcd)
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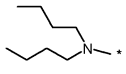
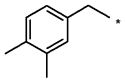
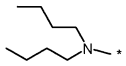
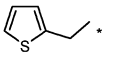
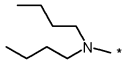
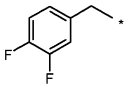
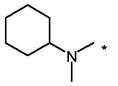
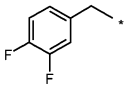
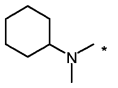
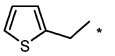
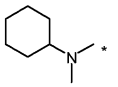
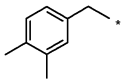
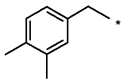
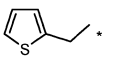
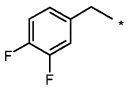
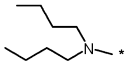
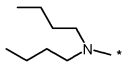
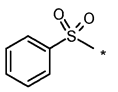
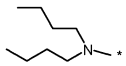
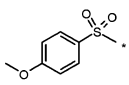
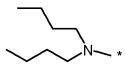
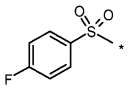
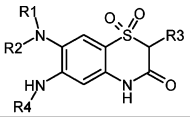
8a		H		100	426	425
8b		H		100	404	403
8c		H		98	434	433
8d		H		92	418	417
8e		H		100	388	387
8f		H		100	410	409
8g		H		99	382	381
8h		H		100	360	359
8i		H		100	390	389
10a		H		93	351	350
12a		H		100	448	447
12b		H		100	478	477
12c		H		100	466	465

[a] Purity determination based on the integration area on HPLC after proper chromatography purification (the detection UV wavelength is at 254 nm).

Table 2. Representative1,1-Dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one Derivatives



Entry	R_1R_2N	R_3	R_4	HPLC purity (%)[a]	MS (found)	MW (calcd)
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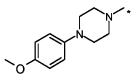
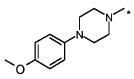
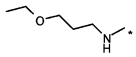
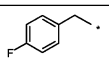
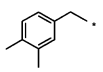
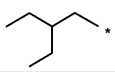
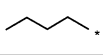
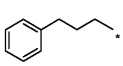
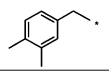
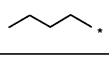
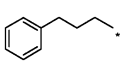
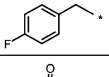
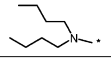
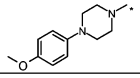
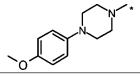
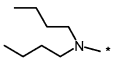
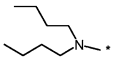
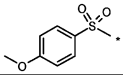
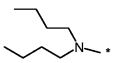
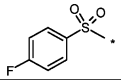
7b		H	H	100	403	402
7c		CH_3	H	100	417	416
7d		H	H	100	314	313
9a		H		100	406	405
9b		H		100	416	415
9c		H		100	382	381
9d		H		100	354	353
9e		H		100	416	415
9f		CH_3		100	430	429
9g		CH_3		100	396	395
9h		CH_3		100	368	367
9i		CH_3		100	430	429
9j		CH_3		100	420	419
11a		H		92	382	381
11b		H		100	445	444
11c		CH_3		100	459	458
13a		H		100	480	479
13b		H		95	510	509
13c		H		96	498	497
13d		CH_3		100	452	451
13e		CH_3		100	482	481

[a] Purity determination based on the integration area on HPLC after proper chromatography purification (the detection UV wavelength is at 254 nm).

Scheme 3. The oxidization step was performed to obtain product **15** from intermediate **14** before the secondary substitution of DFDNB. Compound **15** then was smoothly converted into **16**, which in turn was reduced to offer **6**. The acylation of intermediate **7** then went smoothly as expected. Typical compounds are listed in Tables 1 and 2. The yield of final products (**8**−**13**) ranged from 20 to 60% calculated based on the starting material, DFDNB. The yields were related to the reduction methods in that the yields those using Pd/C−$HCOONH_4$ were higher than those using $SnCl_2 \cdot 2H_2O$.

Conclusion

4H-Benzo[1,4]thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one scaffold compounds were synthesized starting from 1,5-difluoro-2,4-dinitrobenzene in this paper. A cheap oxidant, UHP, was applied for the oxidation of the sulfur atom to the corresponding sulfone compounds with electron-withdrawing groups. Intramolecular cyclization was optimized by the use of a microwave or a strong inorganic base.

Experimental Section

All chemical reagents were purchased from Acros Organics (Geel, Belgium) and were used without further purification. All organic solvents were redistilled after a proper drying procedure. HPLC analysis was performed on a Shimadzu HPLC system equipped with SPD-10A VP detector, LC-10AT VP pump, and a DGU-12A degasser. A gradient was (buffer A, 0.05% TFA/H_2O; buffer B, 0.05%TFA/acetonitrile) B from 5 to 95% in 5 min with a flow rate at 1.0 mL min^{-1}. Auto LC-MS/MS analysis was performed on a Thermo Finnigan, LCQ-Advantage, equipped with Gilson 322 pump, Gilson UV−vis-152 detector, Gilson 215 liquid handler, and a fluent splitter. The elution gradient, flow rate, and detection wavelength are the same as above. Five percent of the eluent was split into an MS system. Mass spectra were recorded in either positive- or negative-ion mode using electrospray ionization. All above HPLC systems were equipped with a fast C18 column (4.6 μm, 4.6 × 50 mm) from DIKMA. All NMR experiments were performed on a Varian Mercury-300 or Mercury-400 NMR spectrometer equipped with an autosampler. Parallel synthesis was conducted on an H+P Labortechnik GmbH parallel synthesizer. Microwave-assisted synthesis was carried out on a CEM microwave synthesizer equipped with an Explorer automatic handle and a Discover vessel.

General Procedure for the Direct Synthesis of Intermediate 3. A solution of 1.0 mmol of primary or secondary amines in 30 mL of THF was added dropwise to a solution of 1.0 mmol of DFDNB and 2.2 equiv of DIPEA in 30 mL of THF. The reaction mixture was stirred at room temperature until the disappearance of DFDNB was detected by HPLC analysis. Then, ethyl α-mercaptoacetate was added, and the mixture was stirred for an additional 2 h at room temperature. The volatiles were removed in vacuo, and 30 mL of water was added to precipitate **2** as a yellow solid. The solid was then collected, after it was thoroughly washed with water, in a yield of over 90% and was used for the next step without physical characterization.

Intermediate **2** in 50 mL of ethanol was completely reduced by a mixture of $SnCl_2 \cdot 2H_2O$ (15 mmol) and 12 N HCl (5 mL) under reflux for 120 min. The reaction mixture was then slowly and carefully poured into a cold 30% aqueous NaOH solution (1000 mL). The pH value was carefully adjusted to 10. The resulting mixture was extracted with DCM (200 mL × 2). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give crude intermediate **3**, which was directly used in the next reaction. Typical compound **3a** was physically characterized after purification on silica gel.

6-Amino-7-piperidin-1-yl-4H-benzo[1,4]thiazin-3-one (3a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.48 (m, 2H), 1.61 (m, 4H), 2.65 (m, 4H), 3.29 (s, 2H), 4.86 (brs, 2H), 6.34 (s, 1H), 6.74 (s, 1H),10.20 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.16, 29.90, 31.59, 52.19,103.84, 117.07, 117.94, 133.90, 135.32, 141.98, 165.47.

General Procedure for the Direct Synthesis of Intermediate 7. Freshly prepared UHP (100 mmol) and trifluoroacetic anhydride (60 mmol) in acetonitrile (30 mL) were slowly added with stirring to a solution of intermediate **2** (4 mmol) in acetonitrile (30 mL) at 0 °C. After the completion of oxidation was detected by HPLC analysis, 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, and dried over anhydrous Na_2SO_4. The solid then was filtered off, and the filtrate was concentrated in vacuo to obtain crude **5**.

$HCOONH_4$ (1.5 g) and 10% Pd/C (200 mg) were added to a solution of crude **5** (1.0 mmol) in THF (15 mL) and ethanol (30 mL) with stirring. The reaction mixture changed from yellow to red and then to colorless in 30 min at room temperature. The catalyst and undissolved excess $HCOONH_4$ were removed by filtration. The filtrate was concentrated in vacuo to produce crude **6**, which was used in the next step without further purification.

Cyclization in the Presence of Sodium Hydride. Sodium hydride (8 mmol) was added to a solution of compound **6** (1 mmol) in dry THF (20 mL); the suspension was then kept at 60 °C under argon protection for 3 h. Anhydrous ethanol was added to quench the reaction. The volatiles were removed in vacuo to give crude **7**.

Microwave-Assisted Cyclization. Compound **6** (1 mmol) was dissolved in dry DMF (8 mL). The reactants were irradiated under a CEM-focused microwave (power = 100 W, ramp time = 10 min, hold time = 60 min, pressure = 100 psi, and T = 140 °C). The reaction was monitored by LC-MS until it was complete. The reaction solution was evaporated in vacuo to dryness to give **7**.

Crude **7** was used in the next step without further purification. Typical compounds of **7** were characterized after purification by silica gel chromatography.

6-Amino-1,1-dioxo-7-piperidin-1-yl-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (7a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.54 (m, 2H), 1.68 (m, 4H), 2.73 (m, 4H), 4.47 (s, 2H), 5.88 (brs, 2H), 6.46 (s, 1H), 7.18 (s, 1H),10.90 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.98, 27.00, 52.22, 57.47, 100.23, 102.33, 111.54, 112.63, 134.19, 148.90, 162.52.

6-Amino-7-[4-(4-methoxy-phenyl)-piperazin-1-yl]-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (7b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.90 (m, 4H), 3.19 (m, 4H), 3.68 (s, 3H), 4.45 (s, 2H), 5.94 (brs, 2H), 6.45 (s, 1H), 6.83 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 7.19 (s, 1H), 10.89 (s, 1H).

6-Amino-7-[4-(4-methoxy-phenyl)-piperazin-1-yl]-2-methyl-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (7c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (d, J = 6.9 Hz, 3H), 2.91 (m, 4H), 3.18 (m, 4H), 3.68 (s, 3H), 4.50 (qu, J = 6.9 Hz, 1H), 5.95 (brs, 2H), 6.44 (s, 1H), 6.83 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 7.20 (s, 1H), 10.87 (s, 1H).

6-Amino-7-(3-ethoxy-propylamino)-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (7d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 (t, 3H, J = 6.6 Hz), 1.84 (qu, 2H, J = 6.6 Hz), 3.06 (m, 2H), 3.43 (m, 4H), 4.35 (s, 2H), 4.70 (m, 1H), 5.71 (brs, 2H), 6.32 (s, 1H), 6.58 (s, 1H),10.65 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.18, 28.76, 40.74, 57.76, 65.34, 67.61, 100.23, 102.31, 112.10, 127.89, 131.55, 142.23,162.13.

General Procedure for the Reductive Amination of Intermediates 3 and 7. A mixture of **3** or **7** (0.1 mmol), aldehyde (0.2 mmol), and 250 μL of AcOH (v/v 5%) in 10 mL of freshly distilled DCM was treated with $NaBH(OAc)_3$ under stirring at room temperature. The reaction was monitored by LC-MS analysis. After the reaction was complete, the solution was quenched with 10 mL of saturated $NaHCO_3$ and extracted with DCM (10 mL × 2). The organic layers was combined, washed with saturated $NaHCO_3$ (10 mL × 2) and brine (10 mL × 2), and dried over anhydrous Na_2SO_4. After removal of the solid through the filtration, the organic solvent was removed under reduced pressure to obtain the crude product. Typical compounds were characterized after purification on silica gel.

7-Dibutylamino-6-(3,4-dimethyl-benzylamino)-4H-benzo[1,4]thiazin-3-one (8a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81 (t, J = 7.2 Hz, 6H), 1.23 (m, 8H), 2.17 (s, 3H), 2.19 (s, 3H), 2.75 (t, J = 7.2 Hz, 4H), 3.32 (s, 2H), 4.15 (d, J = 5.7 Hz, 2H), 5.43 (t, J = 5.7 Hz, 1H), 6.16 (s, 1H), 6.92 (s, 1H), 7.04 (m, 3H), 10.17 (s, 1H).

7-Dibutylamino-6-[(thiophen-2-ylmethyl)-amino]-4H-benzo[1,4]thiazin-3-one (8b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 7.2 Hz, 6H), 1.20 (m, 8H), 2.75 (t, J = 6.9 Hz, 4H), 3.32 (s, 2H), 4.43 (d, J = 6.6 Hz, 2H), 5.70 (t, J = 6.6 Hz, 1H), 6.29 (s, 1H), 6.90 (s, 1H), 6.95 (dd, J = 3.0 Hz, J = 4.8 Hz, 1H), 7.01 (d, J = 2.7 Hz, 1H), 7.36 (dd, J = 4.8 Hz, J = 1.5 Hz, 1H), 10.20 (s, 1H).

7-Dibutylamino-6-(3,5-difluoro-benzylamino)-4H-benzo[1,4]thiazin-3-one (8c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 6.9 Hz, 6H), 1.24 (m, 8H), 2.77 (t, J = 7.2 Hz, 4H), 3.32 (s, 2H), 4.28 (d, J = 6.3 Hz, 2H), 5.97 (t, J = 6.3 Hz, 1H), 6.08 (s, 1H), 6.92 (s, 1H), 7.05 (m, 3H), 10.14 (s, 1H).

7-(Cyclohexyl-methyl-amino)-6-(3,5-difluoro-benzylamino)-4H-benzo[1,4]thiazin-3-one (8d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.70 (m, 10H), 2.20 (s, 3H), 2.64 (m, 1H), 3.32 (s, 2H), 4.28 (d, J = 6.3 Hz, 2H), 5.87 (t, J = 6.3 Hz, 1H), 6.08 (s,1H), 6.89 (s,1H), 7.03 (m, 3H), 10.12 (s,1H).

7-(Cyclohexyl-methyl-amino)-6-[(thiophen-2-ylmethyl)-amino]-4H-benzo[1,4]thiazin-3-one (8e). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.70 (m, 10H), 2.20 (s, 3H), 2.69 (m, 1H), 3.33 (s, 2H), 4.43 (d, J = 6.0 Hz, 2H), 5.63 (t, J = 6.0 Hz, 1H), 6.28 (s,1H), 6.87 (s,1H), 6.95 (dd, J = 4.8 Hz, J = 3.6 Hz, 1H), 7.02 (d, J = 3.6 Hz, 1H), 7.36 (dd, J = 4.8 Hz, J = 1.2 Hz, 1H), 10.12 (s,1H).

7-(Cyclohexyl-methyl-amino)-6-(3,4-dimethyl-benzylamino)-4H-benzo[1,4]thiazin-3-one (8f). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.70 (m, 10H), 2.20 (s, 3H), 2.27 (s, 3H), 2.49 (s, 3H), 2.64 (m, 1H), 3.33 (s, 2H), 4.15 (d, J = 5.7 Hz, 2H), 5.38 (t, J = 5.7 Hz, 1H), 6.18 (s, 1H), 6.89 (s, 1H), 6.94 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 7.5 Hz, 2H), 10.17 (s, 1H).

6-(3,4-Dimethyl-benzylamino)-7-piperidin-1-yl-4H-benzo-[1,4]thiazin-3-one (8g). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62 (brs, 6H), 2.21 (s, 3H), 2.27 (brs, 3H), 2.71 (brs, 4H), 3.31 (s, 2H), 4.17 (d, J = 4.8 Hz, 2H), 5.38 (t, J = 4.8 Hz, 1H), 6.17 (s, 1H), 6.83 (s, 1H), 6.95 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 7.5 Hz, 2H), 10.15 (s, 1H).

7-Piperidin-1-yl-6-[(thiophen-2-ylmethyl)-amino]-4H-benzo[1,4]thiazin-3-one (8h). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64 (brs, 6H), 2.68 (brs, 4H), 3.32 (s, 2H), 4.44 (d, J = 6.0 Hz, 2H), 5.61 (t, J = 6.0 Hz, 1H), 6.29 (s, 1H), 6.81 (s, 1H), 6.96 (dd, J = 5.1 Hz, J = 3.3 Hz, 1H), 7.02 (d, J = 3.3 Hz, 1H), 7.36 (dd, J = 5.1 Hz, J = 1.2 Hz, 1H), 10.18 (s. 1H).

6-(3,5-Difluoro-benzylamino)-7-piperidin-1-yl-4H-benzo-[1,4]thiazin-3-one (8i). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.68 (brs, 6H), 2.71 (brs, 4H), 3.32 (s, 2H), 4.30 (d, J = 6.0 Hz, 2H), 5.81 (t, J = 6.0 Hz, 1H), 6.05 (s, 1H), 6.83 (s, 1H), 7.06 (m, 3H), 10.11(s, 1H).

6-(4-Fluoro-benzylamino)-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (9a). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.79 (t, J = 4.4 Hz, 4H), 3.80 (t, J = 4.4 Hz, 4H), 4.37 (d, J = 6.0 Hz, 2H), 4.43 (s, 2H), 6.17 (s, 1H), 6.76 (t, J = 6.0 Hz, 1H), 7.22 (s, 1H), 7.14∼7.33 (m, 4H), 10.77 (s, 1H).

6-(3,4-Dimethyl-benzylamino)-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (9b). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H), 2.28 (s, 3H), 2.81 (brs, 4H), 3.79 (brs, 4H), 4.30 (d, J = 6.0 Hz, 2H), 4.45 (s, 2H), 6.14 (s, 1H), 6.56 (t, J = 6.0 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H), 7.07 (d, J = 7.5 Hz, 1H), 7.24 (s, 1H), 10.79 (s, 1H).

6-(2-Ethyl-butylamino)-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (9c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, J = 7.5 Hz, 6H), 1.30 (qu, J = 7.5 Hz, 4H), 2.75 (brs, 4H), 3.02 (d, J = 6.0 Hz, 2H), 3.75 (brs, 4H), 4.77 (s, 1H), 5.94 (t, J = 6.0 Hz, 1H), 6.31 (s, 1H), 7.21 (s, 1H), 10.87 (s, 1H).

6-Butylamino-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (9d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.92 (t, J = 7.2 Hz, 3H), 1.33 (m, 2H), 1.55 (qu, J = 7.2 Hz, 2H), 2.73 (brs, 4H), 3.12 (qu, J = 6.3 Hz, 2H), 3.75 (brs, 4H), 4.47 (s, 2H), 5.97 (t, J = 6.3 Hz, 1H), 6.32 (s, 1H), 7.19 (s, 1H), 10.80 (s, 1H).

7-Morpholin-4-yl-1,1-dioxo-6-(3-phenyl-propylamino)-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one (9e). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.90 (qu, J = 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.74 (brs, 4H), 3.12 (qu, J = 6.0 Hz, 2H), 3.75 (brs, 4H), 4.47 (s, 2H), 5.99 (t, J = 6.0 Hz, 1H), 6.32 (s, 1H), 7.20 (s, 1H), 7.13∼7.31 (m, 5H), 10.81 (s, 1H).

6-(3,4-Dimethyl-benzylamino)-2-methyl-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one (9f). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (d, J = 6.8 Hz, 3H), 1.98 (s, 3H), 2.20 (s, 3H), 2.84 (m, 4H), 3.79 (m, 4H), 4.30 (m, 2H), 4.50 (qu, J = 6.8 Hz, 1H), 6.14 (s, 1H), 6.56 (t, J = 6.0 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H), 7.07 (d, J = 7.5 Hz, 1H), 7.25 (s, 1H), 10.78 (s, 1H).

6-(2-Ethyl-butylamino)-2-methyl-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one (9g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (t, J = 7.6 Hz, 6H), 1.33 (m, 4H), 1.38 (d, J = 6.8 Hz, 3H), 1.57 (m, 1H), 2.74 (m, 4H), 3.02 (t, J = 6.0 Hz, 2H), 3.75 (brs, 4H), 4.51 (qu, J = 6.8 Hz, 1H), 5.95 (t, J = 6.0 Hz, 1H), 6.29 (s, 1H), 7.22 (s, 1H), 10.85 (s, 1H).

6-Butylamino-2-methyl-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one (9h). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.92 (t, J = 6.9 Hz, 3H), 1.33 (m, 2H), 1.38 (d, J = 6.9 Hz, 3H), 1.55 (qu, J = 6.9 Hz, 2H), 2.73 (m, 4H), 3.12 (qu, J = 6.3 Hz, 2H), 3.75 (m, 4H), 4.50 (qu, J = 6.9 Hz, 1H), 5.98 (t, J = 6.3 Hz, 1H), 6.30 (s, 1H), 7.20 (s, 1H), 10.80 (s, 1H).

2-Methyl-7-morpholin-4-yl-1,1-dioxo-6-(3-phenyl-propylamino)-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one (9i). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (d, J = 6.9 Hz, 3H), 1.90 (qu, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.75 (m, 4H), 3.13 (q, J = 7.2 Hz, 2H), 3.75 (brs, 4H), 4.51 (q, J = 6.9 Hz, 1H), 6.00 (t, J = 7.2 Hz, 1H), 6.31 (s,1H), 7.22 (s, 1H), 7.23 (m, 5H), 10.08 (s, 1H).

6-(4-Fluoro-benzylamino)-2-methyl-7-morpholin-4-yl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,4]thiazin-3-one (9j). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (d, J = 6.0 Hz, 3H), 2.82 (m, 4H), 3.80 (m, 4H), 4.37 (d, J = 6.4 Hz, 2H), 4.32 (dd, J = 16.0 Hz, J = 6.0 Hz, 1H), 4.40 (dd, J = 16.0 Hz, J = 6.0 Hz, 1H), 6.15 (s, 1H), 6.76 (t, J = 6.4 Hz, 1H), 7.22 (s, 1H), 7.15 (t, J = 8.8 Hz, 2H), 7.34 (t, J = 5.6 Hz, 2H), 10.76 (s, 1H).

General Procedure for the Acetylation of Intermediates 3 and 7. A mixture of **3** or **7** (0.1 mmol) and acetic anhydride (0.3 mmol) in 5 mL of freshly distilled DCM was shaken mechanically at room temperature for 30 min. The conversion was monitored by LC-MS analysis. After the reaction was complete, the volatiles were removed by rotary evaporator under reduced pressure. The residue was purified on silica gel to give pure compounds **10** or **11**.

***N*-(7-Dibutylamino-3-oxo-3,4-dihydro-2H-benzo[1,4]-thiazin-6-yl)-acetamide (10a).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.82 (t, J = 6.9 Hz, 6H), 1.24 (m, 8H), 2.09 (s, 3H), 2.77 (t, J = 6.6 Hz, 4H), 3.40 (s, 2H), 7.18 (s, 1H), 7.89 (s, 1H), 8.88 (s, 1H), 10.46 (s, 1H).

***N*-(7-Dibutylamino-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl)-acetamide (11a).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (t, J = 5.4 Hz, 6H), 1.26 (m, 8H), 2.17 (s, 3H), 2.85 (t, J = 6.9 Hz, 4H), 4.64 (s, 2H), 7.58 (s, 1H), 8.02 (s, 1H), 9.19 (s, 1H), 11.14 (s, 1H).

***N*-{7-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl}-acetamide (11b).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (s, 3H), 2.97 (m, 4H), 3.25 (m, 4H), 3.69 (s, 3H), 4.64 (s, 2H), 6.84 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 7.50 (s, 1H), 8.08 (s, 1H), 9.14 (s, 1H), 11.13 (s, 1H).

***N*-{7-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-2-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl}-acetamide (11c).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42 (d, J = 7.2 Hz, 3H), 2.19 (s, 3H), 2.97 (m, 4H), 3.25 (m, 4H), 3.69 (s, 3H, J = 7.2 Hz), 4.70 (qu, J = 7.2 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 7.51 (s, 1H), 8.07 (s, 1H), 9.14 (s, 1H), 11.13 (s, 1H).

General Procedure for the Sulfonation of Intermediates 3 and 7. A mixture of **3** or **7** (0.1 mmol), pyridine (0.3 mmol), and sulfonyl chloride (0.2 mmol) in 5 mL of freshly distilled DCM was irradiated with CEM-focused microwave irradiation (power = 150 W, ramp time = 10 min, hold time = 60 min, pressure = 100 psi, T = 100 °C). The conversion was monitored by LC-MS analysis. When the reaction was completed, the pyridine hydrochloride was filtered off. The filtrate then was extracted with DCM (10 mL × 2). The combined organic layers were washed with saturated $CuSO_4$ and brine and dried over anhydrous Na_2SO_4. After the filtration, the filtrate was concentrated in vacuo. The residue was purified on silica gel to obtain the pure compounds **12** or **13**.

***N*-(7-Dibutylamino-3-oxo-3,4-dihydro-2H-benzo[1,4]-thiazin-6-yl)-benzenesulfonamide (12a).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.76 (t, J = 6.6 Hz, 6H), 1.16 (m, 8H), 2.60 (t, J = 6.6 Hz, 4H), 3.41 (s, 2H), 7.16 (s, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 2H), 7.90 (d, J = 7.5 Hz, 2H), 8.60 (s, 1H), 10.57 (s, 1H).

***N*-(7-Dibutylamino-3-oxo-3,4-dihydro-2H-benzo[1,4]-thiazin-6-yl)-4-methoxy-benzenesulfonamide (12b).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.75 (t, J = 7.2 Hz, 6H), 1.06 (m, 8H), 2.60 (t, J = 6.6 Hz, 4H), 3.41 (s, 2H), 3.78 (s, 3H), 7.16 (s, 1H), 7.26 (s, 1H), 7.04 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 8.42 (s, 1H), 10.50 (s, 1H).

***N*-(7-Dibutylamino-3-oxo-3,4-dihydro-2H-benzo[1,4]-thiazin-6-yl)-4-fluoro-benzenesulfonamide (12c).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.76 (t, J = 7.2 Hz, 6H), 1.16 (m, 8H), 2.77 (t, J = 7.2 Hz, 4H), 3.42 (s, 2H), 7.17 (s, 1H), 7.23 (s, 1H), 7.41 (m, 2H), 7.95 (m, 2H), 8.56 (s, 1H), 10.56 (s, 1H).

***N*-(7-Dibutylamino-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl)-benzenesulfonamide (13a).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.76 (t, J = 5.4 Hz, 6H), 1.11 (m, 8H), 2.77 (t, 4H), 4.57 (s, 2H), 7.29 (s, 1H), 7.45 (m, 2H), 7.58 (s,1H), 8.02 (m, 3H), 9.32 (m, 1H), 11.22 (s, 1H).

***N*-(7-Dibutylamino-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl)-4-methoxy-benzenesulfonamide (13b).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.76 (t, J = 5.4 Hz, 6H), 1.10 (m, 8H), 2.74 (m, 4H), 3.80 (s, 3H), 4.65 (s, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.43 (s, 1H), 7.55 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 9.05 (s, 1H), 11.22 (s, 1H).

***N*-(7-Dibutylamino-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl)-4-fluoro-benzenesulfonamide (13c).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.76 (t, J = 5.4 Hz, 6H), 1.06 (m, 8H), 2.62 (t, J = 5.4 Hz, 4H), 3.41 (s, 2H), 7.16 (s, 1H), 7.23 (s, 1H), 7.67 (t, J = 8.8 Hz, 2H), 7.96 (dd, J = 8.8 Hz, J = 4.8 Hz, 2H), 8.65 (s, 1H), 10.56 (s, 1H).

***N*-(2-Methyl-7-morpholin-4-yl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl)-benzenesulfonamide (13d).** ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (d, J = 7.2 Hz, 3H), 2.57 (t, J = 4.4 Hz, 4H), 3.70 (t, J = 4.4 Hz, 4H), 4.70 (q, J = 7.2 Hz, 1H), 7.29 (s, 1H), 7.48 (s, 1H), 7.65 ~7.94 (m, 5H), 9.56 (s, 1H), 11.21 (s, 1H).

4-Methoxy-*N*-(2-methyl-7-morpholin-4-yl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazin-6-yl)-benzenesulfonamide (13e). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (d, J = 6.8 Hz, 3H), 2.60 (t, J = 4.4 Hz, 4H), 3.72 (t, J = 4.4 Hz, 4H), 3.80 (s, 3H), 4.70 (qu, J = 6.8 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.30 (s, 1H), 7.48 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 9.38 (s, 1H), 11.21 (s, 1H).

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References and Notes

(1) Dolle, R. E. *J. Comb. Chem.* **2005**, *7* (6), 739−798.
(2) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfieldt, J. *J. Med. Chem.* **1988**, *31*, 2235−2246.
(3) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.
(4) Zhang, L.; Liu, G.; Zhang, S.-D.; Yang, H.-Z.; Li, L.; Wu, X.-H.; Yu, J.; Kou, B.-B.; Xu, S.; Li, J.; Sun, G.-C.; Ji, Y.-F.; Cheng, G.-F. *J. Comb. Chem.* **2004**, *6*, 431−436.
(5) Wu, X.-H.; Liu, G.; Zhang, J.; Wang, Z.-G.; Xu, S.; Zhang, S.-D.; Zhang, L.; Wang, L. *Mol. Diversity* **2004**, *8* (2), 165−174.
(6) Li, L.; Liu, G.; Wang, Z.; Yuan, Y.; Zhang, C.; Tian, H.; Wu, X.; Zhang, J. *J. Comb. Chem.* **2004**, *6*, 811−821.
(7) Zhang, J.; Zhang, L.; Zhang, S.-D.; Liu, G. *J. Comb. Chem.* **2005**, *7*, 657−664.
(8) Liu, G.; Li, L.; Kou, B.-B;.; Zhang, S.-D.; Zhang, L.; Yuan, Y.-Y.; Ma, T.; Shang, Y.; Li, Y.-Ch. *J. Comb. Chem.* **2007**, *9*, 70−78.
(9) Yang, T.-M.; Liu, G. *J. Comb. Chem.* **2007**, *9*, 86−95.
(10) Yuan, Y. Y.; Liu, G.; Li, L.; Wang, Z. G.; Wang, L. *J. Comb. Chem.* **2007**, *9*, 158−170.
(11) Nakao, T.; Obata, M.; Morita, K.; Morimoto, Y.; Anami, K. *J. Phys.* **1988**, *63*, 146872.
(12) Lerch, U.; Henning, R.; Urbach, H.; Kaiser, J. European Patent EP 303180, February 15, 1989.
(13) Matsui, T.; Nakamura, Y.; Ishikawa, H.; Matsuura, A.; Kobayashi, F. *Jpn. J. Pharmacol.* **1994**, *64* (2), 115−24.
(14) Kawashima, Y; Ota, A; Mibu, H. International Patent WO 9405647, March 17, 1994.
(15) Fujita, M.; Ito, S.; Ota, A.; Kato, N.; Yamamoto, K.; Kawashima, Y.; Yamauchi, H.; Iwao, J. *J. Med. Chem.* **1990**, *33* (7), 1898−1905.
(16) Qar, J; Barhanin, J; Romey, G.; Henning, R.; Lerch, U.; Oekonomopulos, R.; Urbach, H.; Lazdunski, M. *Mol. Pharmacol.* **1988**, *33* (4), 363−369.
(17) Peak, D. A.; Watkins, T. I. *J. Chem. Soc.* **1950**, 445−452.
(18) Bordwell, F. G.; Boutan, P. J. *J. Am. Chem. Soc.* **1957**, *79*, 717−722.
(19) Overberger, C. G.; Cummins, R. W. *J. Am. Chem. Soc.* **1953**, *75*, 4250−4254.
(20) DeSimone, R. W.; Petereson, J.; Eddins, C.; Shen, Y. P.; Gustavson, L.; Mach, C.; Hutchinson, A. International Patent WO 03059289, June 24, 2003.

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