Design and Synthesis of Novel Tricycles 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

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This paper reports our recent efforts to develop novel tricycles based on 4H-benzo[1,4]thiazin-3-one (**2**) and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (**3**) using 1,5-difluoro-2,4-dinitrobenzene (**1**). All of these tricycles integrate two privileged structures into one skeleton, including 3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalene-7-one (**4**, **10**, **12**), 5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalene-7-one (**5**, **11**), 3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (**6**), 5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalene-7-one (**7**), 3,8-dihydro-1H-5-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (**8**), and 5,5-dioxo-3,5,6,8-tetrahydro-1H-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (**9**). A typical library of scaffold **5** was synthesized in a parallel solution-phase manner and analyzed by HPLC–UV–MS or HPLC–UV–ELSD method.

Introduction

Benzofused heterocycles containing a sulfur moiety possess many biological activities across wide therapeutic fields, including vasodilator,[1] antidiabetic,[2] anticataract,[3] antiarrhythmic,[4] etc. A "scaffold-directed library synthesis" program has been launched by our group and diverse heterocycles containing a nitrogen or oxygen moiety were successfully developed [5–10] from a commercially available material, 1,5-difluoro-2,4-dinitrobenzene (DFDNB, **1**, Figure 1). We recently reported the parallel solution-phase synthesis of 4H-benzo[1,4]thiazin-3-one (**2**, Figure 1) and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (**3**, Figure 1) derivatives using DFDNB.[11] Benzimidazole,[12] benzimidazolone,[13] thio-benzimidazolone,[14] and benzotriazole[15] occur frequently in biologically active compounds. Integrating such structural fragments into one skeleton can form new scaffolds in a larger chemical space, thus offering more chances for the discovery of drug leads. Our DFDNB chemistry provides an opportunity integrating such privileged structures with 4H-benzo[1,4]thiazin-3-one and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one derivatives. Therefore, eight novel tricycles (**4**–**12**, Scheme 1) were synthesized based on scaffolds **2** and **3**. A chemical library of scaffold **5** was produced in a parallel solution-phase manner.

Results and Discussion

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. Compounds **2** and **3** 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.[11] When these aromatic 6,7-diamines with a sulfur moiety were reacted with aldehydes, sodium nitrite, triphosgene, and carbon disulfide, respectively, eight novel scaffolds **4**–**12** were obtained. The synthetic routes are depicted in Scheme 1.

Reaction of intermediates **2** and **3** with aldehydes in a weakly acidic solution (5% AcOH in DMF) at room temperature gave the corresponding fused imidazoles **4** and **5** at approximate 70% in yields. Typically synthesized compounds are listed in Table 1. Treatment of **2** and **3** with sodium nitrite in DCM and 50% aqueous acetic acid (v/v = 5:1) offered the desired triazoles **6** and **7** (Table 2) with the yields ranging from 40% to 85%.

When intermediate **2** was reacted with excess triphosgene or carbon disulfide in the presence of triethylamine, novel scaffolds **8** and **10** were obtained respectively at approximate 80% in yields. Typical compounds of **8** and **10** are listed in Tables 3 and 4. Continuous S-alkylation of **10** with alkyl bromides in the presence of triethylamine afforded **12** derivatives (Table 4), yields of which ranged from 60% to 80% based on **2**. Such derivation introduced one more diversity point of **12**.

The reaction of intermediate **3** with triphosgene or carbon disulfide using the same treatment as that of intermediate **2** did not give the desired scaffold (**9** or **11**) compounds. We tried various harsh conditions, but most of them failed or only gave poor yield. The conditions we investigated are listed in Tables 5 and 6. These phenomena are deduced as a result of the reduced nucleophilicity of the aromatic 6-amino group, which locates at the para- position of the strong electron-withdrawing sulfone group.

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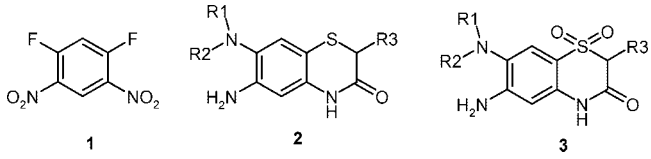


Figure 1. Structures of **1**, **2**, and **3** derivatives.

Triphosgene is a safe and highly efficient replacer of the toxic phosgene. One molar triphosgene reacts with three molar nucleophilic reagents and releases three molar of hydrogen chloride (HCl), and a base without nucleophilicity is necessary to neutralize the byproduct HCl.[16] Based on the understanding of reaction mechanism, we added triethylamine in the reaction system (Table 5, entries 1–8). Prolongation of the reaction period at room temperature did not give any detectable product by HPLC–MS analysis (entries 1, 2, and 3). Increasing the reaction temperature to reflux in DCM or DMF only resulted in trace amounts of anticipated products (entries 4, 5, and 6). Even the hardest condition under microwave-assistance did not significantly convert **3** into **9** (entries 7 and 8). However, when the reaction was performed in toluene even without addition of an organic base, a 100% conversion rate of **3** into **9** was fortunately gained under microwave-assistance (entry 9). After evaporation of the volatiles, the only peak in the HPLC chromatograph corresponded to the aimed product by HPLC–MS analysis (Figure 2). The mechanism of this reaction is still not well understood.

Similarly, the conditions of intermediate **3** reacted with CS_2 to offer scaffold **11** were systematically studied, and these are listed in Table 6. These include using various solvents, the addition of organic base (Et_3N) and inorganic alkali (K_2CO_3 and KOH), increasing the reaction temperature, and microwave-assistance. We only found that KOH in DMF (entry 10) slightly improved the conversion rate by HPLC–MS analysis. It was deduced that the proton of 6-amino group of **3** was not completely removed by inorganic alkali KOH before the addition of CS_2. The reaction procedure was then adjusted. Compound **3** was added to the suspension mixture of KOH in DMF, which was stirred for at least 30 min to obtain the highest concentration of KOH in DMF. The reaction mixture became deep red immediately and was continuously stirred for an additional 30 min at room temperature to completely abstract protons of **3**. CS_2 was finally added and the reaction was monitored by HPLC–MS analysis. This improved procedure finally gave the anticipated product as indicated in Figure 3. Typical compounds **9** and **11** are listed in Tables 3 and 4.

Preparation of 5,5-Dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalene-7-one (5) Library. Scaffold **5** possesses three diversity points, which are introduced by primary amines (R_1NH_2), ethyl mercaptoacetate ($HSCH(R_2)COOC_2H_5$), and aldehydes (R_3CHO). To prepare scaffold **5** library, building blocks were carefully selected following these rules: (1) reagents containing incompatible groups (such as benzyl, sulfur atom, etc.) with the Pd/C-$HCOONH_4$ reduction method were excluded; (2) to obtain the maximum diverse substitution at each diversity point; (3) easy removal of excess reagents. Thus, 22 primary amines, 2 ethyl mercaptoacetates, and 72 aldehydes from our stock reagents (Table 7) were finally selected to construct scaffold **5** library in a solution-phase manner.

The procedure of library synthesis is depicted in Figure 4. At step I, DFDNB was substituted by two nucleophilic reagents in high yields. The oxidization step II was carried out in a parallel manner. The intermediates were simultaneously extracted using phase separators with DCM against water. The organic layer was evaporated *in vacuo*, and the residue was directly used in the next step. At step III of reduction, the aromatic dinitro groups were reduced using $HCOONH_4$ with Pd/C on a H+P Labortechnik GmbH parallel synthesizer. The insoluble catalyst and impurities were filtered off using our parallel filtration apparatus.[17] At step IV, two methods were employed to achieve cyclization of the reduction intermediates. When NaH was used to promote the cyclization, excess inorganic base after reaction had to be quenched with water and washed away using phase separators before step V. When the cyclization was carried out under microwave-assistance, a CEM autosampler microwave synthesizer (Explore) was adopted, which allowed synthesizing the cyclized compounds individually but automatically. The solvent and other volatiles were removed by evaporation under reduced pressure. Intermediates **3** were then redissolved in DMF containing acetic acid and distributed into 70 precoded reaction vessels of the H+P Labortechnik GmbH parallel synthesizer. Subsequently, the aldehydes were added and the reactions were monitored by HPLC–MS analysis. When the most difficult reactions were not progressing, the reactions were stopped. PS-NH_2 scavenger resin was used to remove the excess aldehydes.

Two thousand compounds were synthesized in a parallel manner. All of them were analyzed by our fast HPLC–UV–MS/MS or HPLC–UV–ELSD system. The analysis results of typical compounds are indicated in Figure 5. Among them, 52% of compounds were over 85% in purity by HPLC analysis with a UV detector at 254 nm and an MS or ELSD detector. The total yields of the library members ranged from 10% to 25% based on the starting material of DFDNB. The compounds over 85% in purity were then reorganized as a chemical library for the further biological screening. Fortunately, high-throughput screening did identify some hits, which will be reported separately.

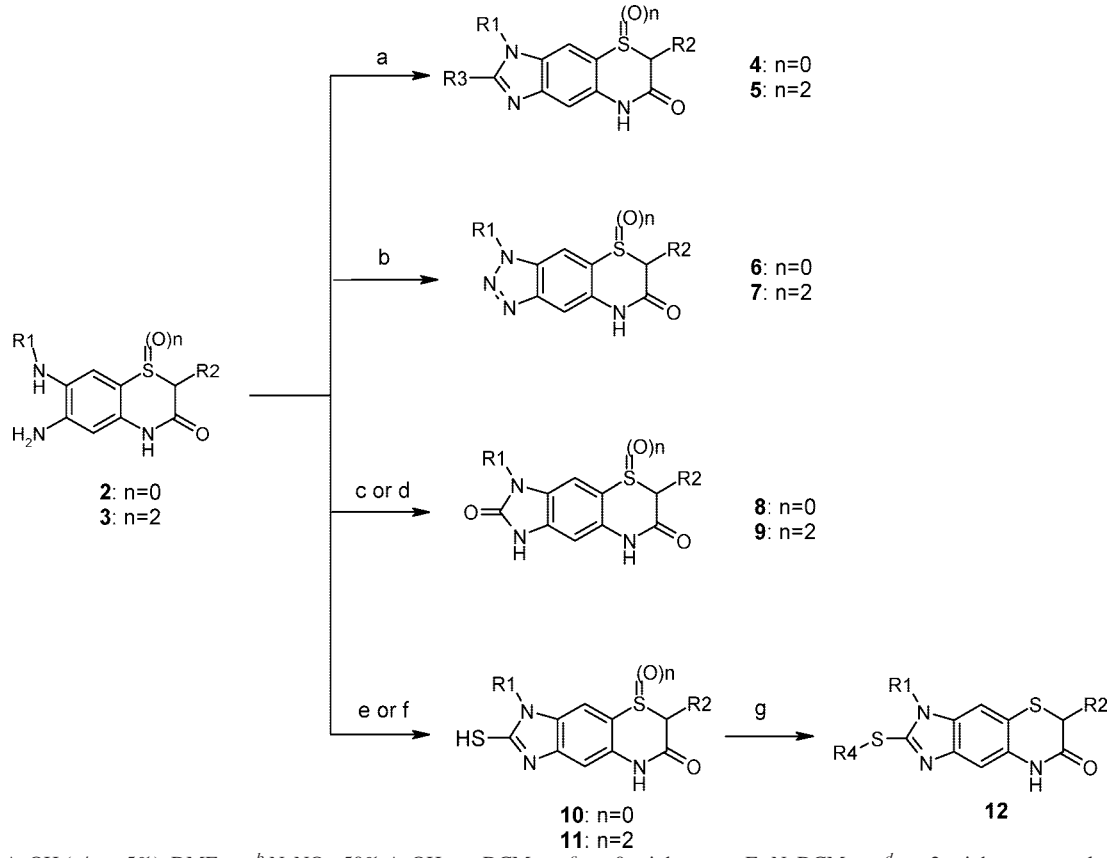
Conclusion

4H-Benzo[1,4]thiazin-3-one (**2**) and 1,1-dioxo-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one (**3**) are privileged structures with multiple biological activities. Starting from **2** and **3**, eight novel tricycles **4**–**12** which are integrated with imidazole, carbonylimidazole, mercaptoimidazole, and triazole were developed. Furthermore, a typical library of scaffold **5** was synthesized in a parallel solution-phase manner from the starting material of DFDNB (**1**) and analyzed by HPLC–UV–MS or HPLC–UV–ELSD system.

Experimental Section

All chemical reagents were purchased from Acros Organics (Geel, Belgium) and used without further purification. All organic solvents were redistilled after the proper drying procedure. Microwave-assistance synthesis was carried out

Scheme 1. Synthetic Outlines of Novel Tricyclic Scaffolds Based on 4H-Benzo[1,4]thiazin-3-one and 1,1-Dioxo-1,4-dihydro-2H-1,6-benzo[1,4]thiazin-3-one



[a] R_3CHO, AcOH (v/v = 5%), DMF, r.t. [b] $NaNO_2$, 50% AcOH aq., DCM, r.t. [c] *n*= 0: triphosgene, Et_3N, DCM, r.t. [d] *n*= 2: triphosgene, toulene, microwave-assistance (power = 150 w, pressure = 100 psi, *T* = 80 °C, *t*= 1 h). [e] *n*= 0: CS_2, Et_3N, EtOH, r.t. [f] *n*= 2: CS_2, KOH, DMF, r.t. [g] R_4Br, Et_3N, EtOH, r.t.

on a CEM microwave synthesizer equipped with an Explorer automatic handler and a Discover vessel. HPLC analysis was carried out using a Shimadzu HPLC system equipped with an SPD-10A VP detector, an LC-10AT VP pump, and a DGU-12A degasser. The general gradient was as follows: buffer A, 0.05% TFA/H_2O; B, 0.05%TFA/acetonitrile; B from 5% to 95% in 5 min with a flow rate of 1.0 mL/min. Auto HPLC–UV–MS analysis was performed on a Thermo Finnigan LCQ-Advantage mass spectrometer equipped with a Gilson 322 pump, a Gilson UV/vis-152 detector, a Gilson 215 liquid handler, and a fluent splitter (5% effluent was split into MS system). All above HPLC systems were equipped with a Kromasil C18 column (4.6 μm, 4.6 × 50 mm) from DIKMA. All NMR experiments were performed on a Varian Mercury 300, 400, or Inova 500 MHz NMR spectrometer equipped with an auto sampler. Parallel synthesis was carried out on an H+P Labortechnik GmbH parallel synthesizer. Phase separators were purchased from Argonaut Inc. (Mid. Glamorgan, U.K.).

General Procedure for the Synthesis of Scaffolds 4 and 5. Intermediates **2** and **3** were prepared according to previously reported methods.[11] To a solution of intermediates **2** or **3** (0.1 mmol) in 5 mL of anhydrous DCM was added aldehyde (0.3 mmol) and acetic acid (250 μL) at room temperature under mechanical shaking. When the reaction was complete as indicated by HPLC–MS analysis, the reaction mixture was evaporated *in vacuo* to dryness. The crude residue was redissolved in 15 mL of DCM and then washed with saturated $NaHCO_3$ solution (10 mL × 2) and brine (10 mL × 2). After being dried over anhydrous Na_2SO_4, the filtrate was concentrated *in vacuo* to give **4** or **5**. The final products were purified on a silica gel column eluting with ethyl acetate and petroleum ether (v/v = 1:2) and characterized by NMR spectrometry.

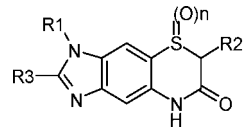
2-(4-Isopropyl-phenyl)-3-(2-methyl-benzyl)-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.20 (d, *J* = 7.2 Hz, 6H), 2.30 (s, 3H), 2.91 (m, 1H), 3.44 (s, 2H), 5.47 (s, 2H), 6.33 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.33–7.36 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 10.50 (s, 1H).

3-(2-Methyl-benzyl)-2-thiophen-2-yl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.42 (s, 3H), 3.45 (s, 2H), 5.64 (s, 2H), 6.17 (d, *J* = 7.6 Hz, 1H), 6.9–7.30 (m, 6H), 7.33 (s, 1H), 7.53 (s, 1H), 10.53 (s, 1H).

3-(2-Methyl-benzyl)-2-(5-nitro-furan-2-yl)-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4c). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.42 (s, 3H), 3.50 (s, 2H), 5.79 (s, 2H), 6.07 (d, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.27 (m, 2H), 7.40 (s, 1H), 7.68 (s, 1H), 7.79 (d, *J* = 4.0 Hz, 1H), 10.63(s, 1H).

2-(3,4-Dimethyl-phenyl)-3-(2-methyl-benzyl)-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4d). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.05 (s, 3H), 2.06 (s, 3H), 2.20 (s, 3H), 3.45 (s, 2H), 5.23 (s, 2H), 6.36 (d, *J* =

Table 1. Representative Compounds Based on Scaffolds **4** and **5**



4: n=0
5: n=2

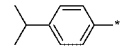
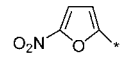
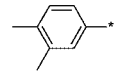
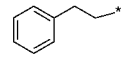
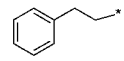
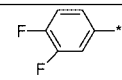
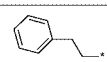
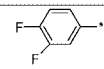
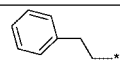
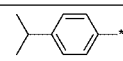
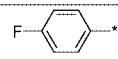
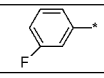
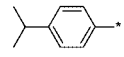
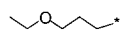
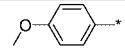
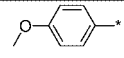
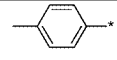
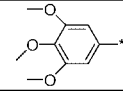
Entry	n	R1	R2	R3	HPLC purity a	MS (found [b])	MW (calcd.)
4a	0		H		98%	428	427
4b	0		H		100%	392	391
4c	0		H		99%	421	420
4d	0		H		100%	414	413
4e	0		H		100%	414	413
4f	0		H		100%	380	379
4g	0		H		100%	358	357
4h	0		H		100%	388	387
4i	0		H		100%	318	317
4j	0		CH_3		100%	436	435
4k	0		CH_3		99%	442	441
5a	2		CH_3		90%	388	387
5b	2		CH_3		100%	414	413
5c	2		CH_3		100%	438	437
5d	2		H		100%	430	429
5e	2		CH_3		100%	400	399
5f	2		CH_3		100%	384	383
5g	2		H		98%	472	471

Table 1. Continued

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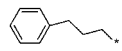
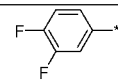
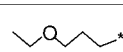
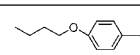
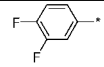
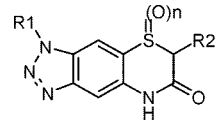
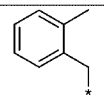
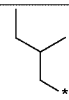
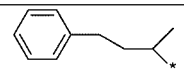
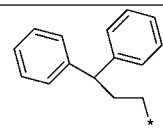
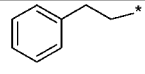
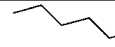
5i	2		H		100%	468	467
5j	2		H		100%	406	405
5k	2		CH_3		100%	468	467
5l	2		CH_3		100%	390	389
5m	2		H		97%	418	417

[a] Purity determination is based on the integration area on HPLC after proper chromatography purification. The UV detection wavelength is 254 nm. [b] Found molecular weight by positive-ion scanning using ESI–MS.

Table 2. Representative Compounds Based on Scaffolds **6** and **7**

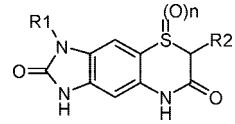


6: n=0
7: n=2

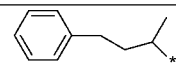
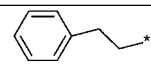
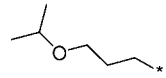
Entry	n	R_1	R_2	HPLC purity [a]	MS (found [b])	MW (calcd.)
6a	0		H	97%	249	248
6b	0		H	98%	311	310
6c	0		H	100%	277	276
6d	0		H	100%	339	338
6e	0		H	99%	401	400
6f	0		CH_3	100%	325	324
6g	0		CH_3	100%	291	290
7a	2		H	96%	309	308
7b	2		CH_3	100%	323	322

[a] Purity determination is based on the integration area on HPLC after proper chromatography purification. The UV detection wavelength is 254 nm. [b] Found molecular weight by positive-ion scanning using ESI–MS.

Table 3. Representative Compounds Based on Scaffolds **8** and **9**



8: n=0
9: n=2

Entry	n	R1	R2	HPLC purity [a]	MS (found [b])	MW (calcd.)
8a	0		H	98%	354	353
8b	0		CH_3	100%	306	305
8c	0		CH_3	99%	340	339
9a	2		H	100%	322 [c]	323
9b	2		H	100%	294 [c]	295
9c	2		H	100%	354	353

[a] Purity determination is based on the integration area on HPLC after proper chromatography purification. The UV detection wavelength is 254 nm. [b] Found molecular weight by positive-ion scanning using ESI–MS. [c] Found molecular weight by negative-ion scanning using ESI–MS.

7.6 Hz, 1H), 6.99–7.18 (m, 6H), 7.33 (s, 1H), 7.45 (s, 1H), 10.49 (s, 1H).

3-(2-Methyl-benzyl)-2-phenethyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4e). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.33 (s, 3H), 2.98 (m, 4H), 3.27 (s, 2H), 5.33 (s, 2H), 6.11 (d, J = 7.2 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.14–7.22 (m, 8H), 7.26 (s, 1H), 7.34 (s, 1H), 10.42 (s, 1H).

3-(2-Methyl-butyl)-2-phenethyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4f). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.72 (d, J = 6.8 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H), 1.11 (m, 1H), 1.23 (m, 1H),1.76 (m, 1H), 3.06 (m, 4H), 3.43 (s, 2H), 3.84 (dd, J = 14.8 Hz, J = 7.2 Hz, 1H), 3.93 (dd, J = 14.8 Hz, J = 7.2 Hz, 1H), 7.16–7.26 (m, 5H), 7.18 (s, 1H), 7.48 (s, 1H), 10.41 (s, 1H).

3-(2-Methyl-butyl)-2-thiophen-2-yl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4g). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.74 (d, J = 6.8 Hz, 3H), 0.79 (t, J = 7.6 Hz, 3H), 1.14 (m, 1H), 1.29 (m, 1H), 1.87 (m, 1H), 3.27 (s, 2H), 4.25 (dd, J = 14.8 Hz, J = 7.2 Hz, 1H), 4.35 (dd, J = 14.8 Hz, J = 7.2 Hz, 1H), 7.24 (s, 2H), 7.69 (m, 3H), 10.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 11.01, 16.25, 26.08, 29.45, 34.80, 49.73, 106.20, 109.35, 115.12, 127.69, 128.37, 129.37, 132.43, 133.08, 133.26, 141.42, 147.67, 165.70.

2-(3,4-Difluoro-phenyl)-3-(2-methyl-butyl)-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4h). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.68 (d, J = 7.2 Hz, 3H), 0.67 (t, J = 7.2 Hz, 3H), 0.93 (m, 1H), 1.13 (m, 1H), 1.64 (m, 1H), 3.47 (s, 2H), 4.10 (dd, J = 14.8 Hz, J = 7.6 Hz, 1H), 4.24 (dd, J = 14.8 Hz, J = 7.6 Hz, 1H), 7.28 (s, 1H), 7.62 (m, 2H), 7.71 (s, 1H), 7.87 (m, 1H), 10.48 (s, 1H).

3-(2-Methyl-butyl)-2-propyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4i). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.78 (d, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H), 1.17 (m, 1H), 1.28 (m, 1H), 1.85 (m, 3H), 2.75 (t, J = 7.2 Hz, 2H), 3.42 (s, 2H), 3.90 (dd, J = 14.8 Hz, J = 7.6 Hz, 1H), 4.01 (dd, J = 14.8 Hz, J = 7.6 Hz, 1H), 7.16 (s, 1H), 7.47 (s, 1H), 10.38 (s, 1H).

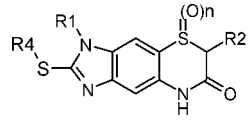
2-(3,4-Difluoro-phenyl)-6-methyl-3-phenethyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4j). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.22 (d, J = 7.2 Hz, 3H), 2.91 (t, J = 6.8 Hz, 2H), 3.65 (qu, J = 7.2 Hz, 1H), 4.48 (m, 2H), 6.80 (m, 2H), 7.10 (m, 3H), 7.27 (s, 1H), 7.56–7.34 (m, 3H), 7.72 (s, 1H), 10.52 (s, 1H).

2-(4-Isopropyl-phenyl)-6-methyl-3-phenethyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (4k). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.24 (d, J = 6.8 Hz, 6H), 1.33 (d, J = 7.2 Hz, 3H), 2.95 (m, 3H), 3.62 (qu, J = 7.2 Hz, 1H), 4.43 (m, 2H), 6.95 (m, 2H), 7.16 (m, 3H), 7.26 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.62 (s, 1H), 10.49 (s, 1H).

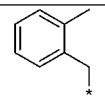
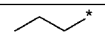
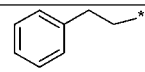
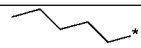
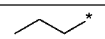
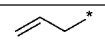
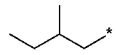
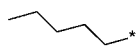
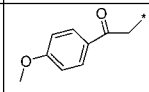
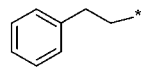
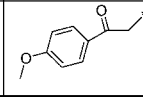
2-(4-Fluoro-phenyl)-6-methyl-5,5-dioxo-3-propyl-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.71 (t, J = 7.2 Hz, 3H), 1.47 (d, J = 7.2 Hz, 3H), 1.63 (m, 2H), 4.37 (m, 2H), 4.74 (m, 1H), 7.44 (dd, J = 8.8 Hz, J = 9.2 Hz, 2H), 7.45 (s, 1H), 7.86 (dd, J = 8.8 Hz, J = 5.6 Hz, 2H). 8.27 (s, 1H), 11.16 (s, 1H).

3-Cyclopentyl-2-(3-fluoro-phenyl)-6-methyl-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.47 (d, J = 6.8 Hz, 3H), 1.69 (m, 2H), 1.93 (m, 2H), 2.17 (m,

Table 4. Representative Compounds Based on Scaffolds **10**, **11**, and **12**



10, **12**: n=0
11: n=2

Entry	n	R1	R2	R4	HPLC purity [a]	MS (found [b])	MW (calcd.)
10a	0		H	H	100%	342	341
10b	0		H	H	100%	280	279
10c	0		CH_3	H	100%	356	355
10d	0		CH_3	H	98%	322	321
11a	2		CH_3	H	93%	326	325
11b	2		CH_3	H	98%	354	353
11c	2		H	H	100%	340	339
12a	0		H		99%	320	319
12b	0		H		100%	348	347
12c	0		CH_3		100%	470	469
12d	0		CH_3		100%	504	503

[a] Purity determination is based on the integration area on HPLC after proper chromatography purification. The UV detection wavelength is 254 nm. [b] Found molecular weight by positive-ion scanning using ESI–MS.

Table 5. Investigated Conditions of Synthesizing Scaffold **9** Compounds[a]

entry	solvent	base	temperature	reaction period	result
1	DCM	Et_3N	r. t.	1 h	no
2	DCM	Et_3N	r. t.	3 h	no
3	DCM	Et_3N	r. t.	5 h	no
4	DCM	Et_3N	50 °C	1 h	trace
5	DCM	Et_3N	50 °C	3 h	trace
6	DMF	Et_3N	140 °C	2 h	trace
7	DCM	Et_3N	MW[b]	1 h	little
8	DCM	Et_3N	MW[b]	2 h	little
9	toluene		MW[b]	1 h	complete

[a] All obtained results were determined by HPLC–MS analysis. [b] Microwave irradiation at 150 W, 80 °C.

Table 6. Investigated Conditions of Synthesizing Scaffold **11** Compounds[a]

entry	solvent	base	temperature	reaction period	result
1	C_2H_5OH	Et_3N	r. t.	1–5 h	no
2	C_2H_5OH	Et_3N	85 °C	1–3 h	no
3	C_2H_5OH	Et_3N	MW[b]	1 h	no
4	CH_3COCH_3	K_2CO_3	r. t.	1–5 h	trace
5	CH_3COCH_3	K_2CO_3	70 °C	1–3 h	trace
6	CH_3COCH_3	K_2CO_3	MW[b]	1 h	trace
7	C_2H_5OH	KOH	r. t.	1–5 h	trace
8	C_2H_5OH	KOH	85 °C	1–3 h	trace
9	C_2H_5OH	KOH	MW[b]	1 h	trace
10	DMF	KOH	r. t.	1–5 h	little to complete[c]

[a] All obtained results were determined by LC–MS analysis. [b] Microwave irradiation at 150 W, 80 °C. [c] The complete conversion rate was obtained when the special procedure of adding the reaction materials was adopted.

4H), 4.74 (qu, J = 7.2 Hz, 1H), 4.90 (qu, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.55 (m, 3H), 7.67 (m, 1H), 7.97 (s, 1H), 11.19 (s, 1H).

3-Cyclopentyl-2-(4-isopropyl-phenyl)-6-methyl-5,5-dioxo-3,5,6,8-tetrahydro-5λ⁶-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5c). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.26 (d, J = 6.8 Hz, 3H), 1.46 (d, J = 6.8 Hz, 6H), 1.70 (m, 2H), 1.96 (m, 2H), 2.12 (m, 4H), 3.00 (qu, J = 7.2 Hz, 1H), 4.94 (qu, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 11.18 (s, 1H).

3-(3-Ethoxy-propyl)-2-(4-methoxy-phenyl)-5,5-dioxo-3,5,6,8-tetrahydro-5λ⁶-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5d). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.99 (t, J = 7.2 Hz, 3H), 1.88 (m, 2H), 3.18 (m, 2H), 3.84 (s,

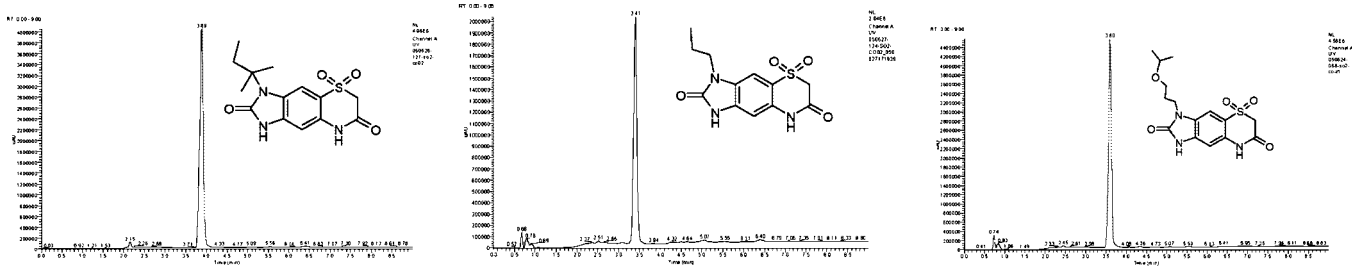


Figure 2. LC–MS analysis indicated that the unique scaffold **9** compounds were obtained under the entry 9 condition of Table 5.

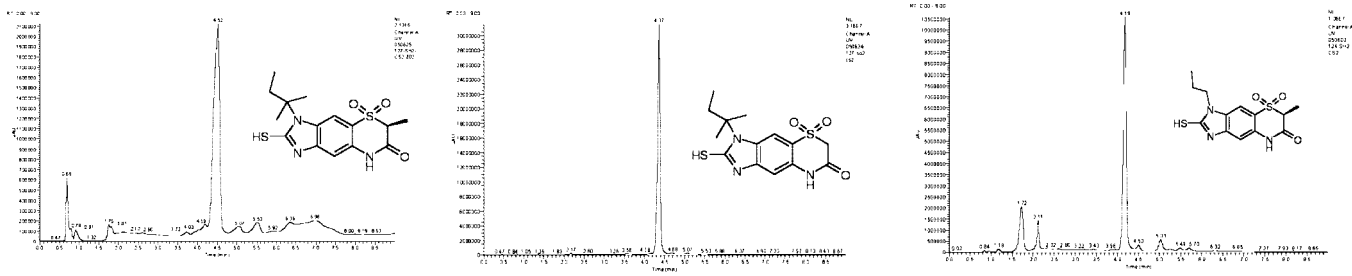


Figure 3. LC–MS analysis indicated that the unique scaffold **11** compounds were gained with the optimized reaction procedure in the presence of KOH.

3H), 4.47 (t, $J = 7.2$ Hz, 2H), 4.68 (s, 2H), 7.12 (d, $J = 8.8$ Hz, 2H), 7.44 (s,1H), 7.78 (d, $J = 8.8$ Hz, 2H), 8.16 (s, 1H), 11.14 (s, 1H).

2-(4-Methoxy-phenyl)-6-methyl-5,5-dioxo-3-propyl-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5e). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.73 (t, $J = 7.2$ Hz, 3H), 1.46 (d, $J = 7.2$ Hz, 2H), 1.65 (m, 2H), 3.85 (s, 3H), 4.37 (m, 2H), 4.72 (qu, $J = 7.2$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.42 (s, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 8.23 (s, 1H), 11.13 (s, 1H).

6-Methyl-5,5-dioxo-3-propyl-2-p-tolyl-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5f). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.71 (t, $J = 7.2$ Hz, 3H), 1.46 (d, $J = 7.2$ Hz, 3H), 1.65 (m, 2H), 2.38 (s, 3H), 4.37 (m, 2H), 4.73 (qu, $J = 7.2$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.44 (s, 1H), 7.68 (d, $J = 8.0$ Hz, 2H), 8.25 (s, 1H), 11.14 (s, 1H).

3-Cyclopentyl-5,5-dioxo-2-(3,4,5-trimethoxy-phenyl)-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5g). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.74–2.15 (m, 8H), 3.85 (s, 9H), 4.72 (s, 2H), 5.02 (m, 1H), 6.95 (s, 2H), 7.49 (s, 1H), 7.93 (s, 1H), 11,17 (s, 1H).

3-Cyclopentyl-5,5-dioxo-2-propyl-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5h). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.97 (d, $J = 7.6$ Hz, 3H), 1.76 (m, 4H), 1.97 (m, 4H), 2.11 (m, 2H), 2.90 (m, 2H), 4.66 (s, 2H), 4.98 (m, 1H), 7.37 (s, 1H), 7.81 (s, 1H), 11.09 (s, 1H).

2-(3,4-Difluoro-phenyl)-5,5-dioxo-3-(3-phenyl-propyl)-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5i). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.95 (t, $J = 7.6$ Hz, 2H), 2.51 (m, 2H), 4.37 (t, $J = 7.6$ Hz, 2H), 4.68 (s, 2H), 7.04 (d, $J = 7.6$ Hz, 2H), 7.19 (m, 3H), 7.47 (s, 1H), 7.57 (m, 2H), 7.82 (m, 1H), 8.26 (s, 1H), 11.12 (s, 1H).

3-(3-Ethoxy-propyl)-5,5-dioxo-2-thiophen-2-yl-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5j). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.10 (t, $J = 6.8$ Hz, 3H), 2.01 (m, 2H), 3.30 (m, 4H), 4.63 (m, 2H), 4.69 (s, 2H), 7.30 (t, $J = 4.4$ Hz, 1H), 7.41 (s, 1H), 7.90 (d, $J = 4.8$ Hz, 2H), 8.16 (s, 1H), 11.16 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 15.02, 29.47, 41.73, 56.18, 65.54, 66.07, 106.24, 107.15, 121.42, 128.77, 128.94, 130.91, 131.44, 131.52, 132.42, 146.13, 150.89, 161.88.

2-(4-Butoxy-phenyl)-3-cyclopentyl-6-methyl-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5k). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.96 (t, $J = 6.8$ Hz, 3H), 1.42 (m, 5H), 1.73 (m, 4H), 1.94 (m, 2H), 2.12 (m, 4H), 4.06 (t, $J = 5.6$ Hz, 2H), 4.73 (m, 1H), 4.94 (qu, $J = 8.8$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.45 (s,1H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.91 (s, 1H), 11.16 (s, 1H).

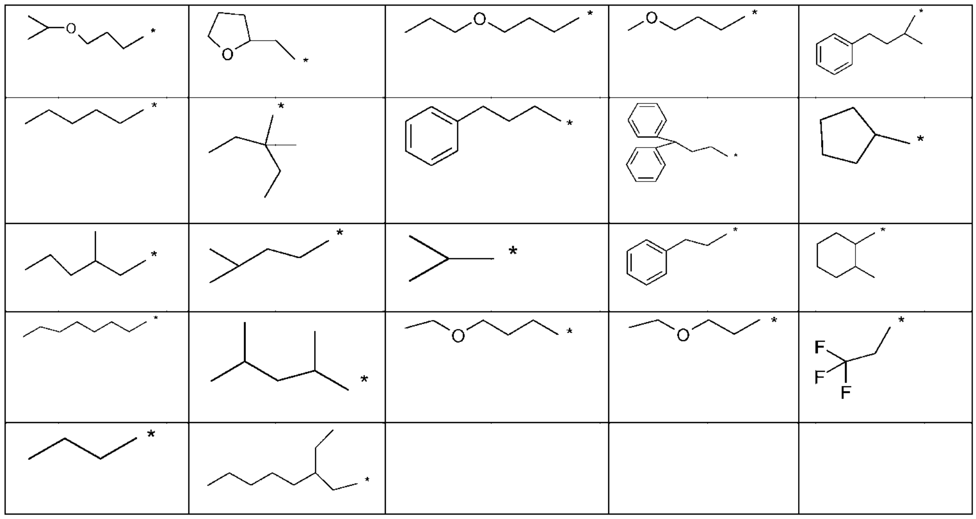
3-Cyclopentyl-2-(1-ethyl-propyl)-6-methyl-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5l). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.75 (q, $J = 7.2$ Hz, 6H), 1.45 (d, $J = 6.8$ Hz, 3H), 1.74 (m, 6H), 1.97–2.08 (m, 6H), 3.10 (m, 1H), 4.71 (q, $J = 7.2$ Hz, 1H), 5.12 (qu, $J = 8.8$ Hz, 1H), 7.39 (s, 1H), 7.82 (s, 1H), 11.11 (s, 1H).

3-Cyclopentyl-2-(3,4-difluoro-phenyl)-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (5m). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.69 (m, 2H), 1.93 (m, 2H), 2.14 (m, 4H), 4.73 (s, 2H), 4.90 (m, 1H), 7.50 (s, 1H), 7.58 (m, 1H), 7.68 (m, 1H), 7.82 (m, 1H), 7.95 (s, 1H), 11.19 (s, 1H).

General Procedure for the Synthesis of Scaffolds 6 and 7. Intermediates **2** or **3** (0.1 mmol) were dissolved in a mixture of DCM (5 mL) and 50% aqueous acetic acid (1 mL). Sodium nitrite (0.2 mmol) was then added at room temperature and the mixture was kept stirring for less than 30 min. When the reaction was complete as indicated by HPLC–MS analysis, 2 mL of water was added and extracted with DCM (10 mL × 2). The organic layer was combined and washed with saturated $NaHCO_3$ solution (10 mL × 2) and brine (10 mL × 2), and dried over anhydrous Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether to give pure com-

Table 7. Building Blocks Used To Synthesize Library of Scaffold **5**

Primary amines (R_1NH_2):



Mercaptoacetates ($HSCH(R_2)COOC_2H_5$):

H	CH_3			

Aldehydes (R_3CHO):

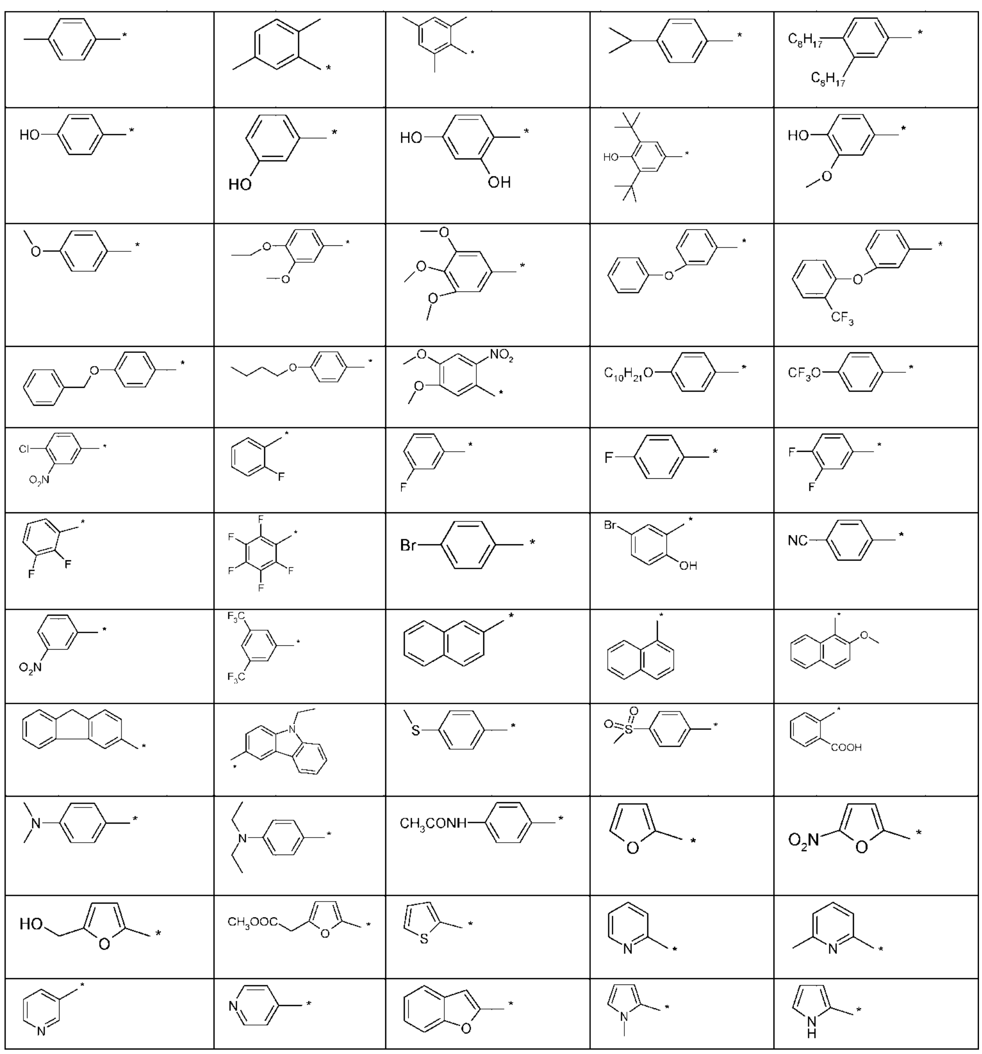
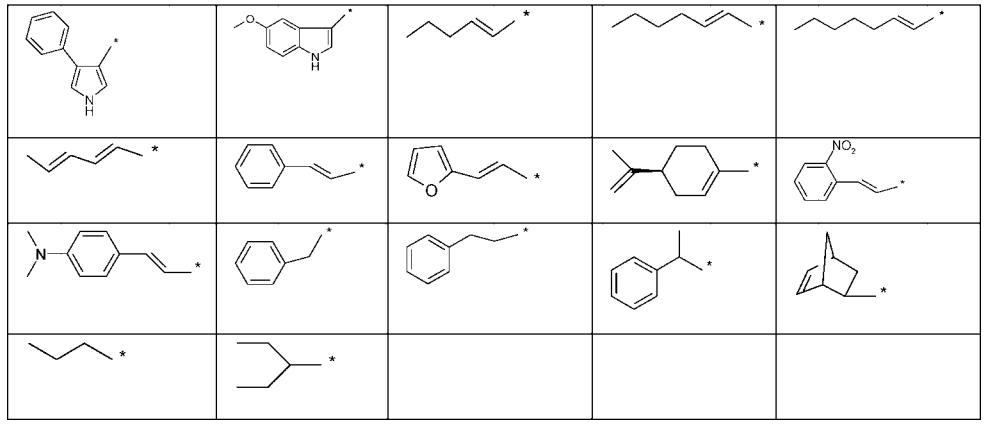


Table 7. Continued

Aldehydes (R_3CHO):



pounds **6** or **7**. Typical compounds were characterized by NMR spectrometry and are listed as below.

3-Propyl-3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta [b]naphthalen-7-one (6a). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.97 (t, J = 6.9 Hz, 3H), 2.03 (m, 2H), 3.51 (s, 2H), 4.56 (t, J = 7.5 Hz, 2H), 7.54 (s, 1H), 8.97 (s, 1H), 10.70 (s, 1H).

3-(2-Methyl-benzyl)-3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (6b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.31 (s, 3H), 3.54 (s, 2H), 5.74 (s, 2H), 6.90–7.20 (m, 4H), 7.54 (s, 1H), 7.82 (s, 1H), 10.75 (s, 1H).

3-(2-Methyl-butyl)-3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (6c). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.79 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 1.14–1.32 (m, 2H), 2.03 (m, 1H), 3.55 (s, 2H), 4.44 (dd, J = 14.0 Hz, J = 7.2 Hz, 1H), 4.53 (dd, J = 14.0 Hz, J = 7.2 Hz, 1H), 7.50 (s, 1H), 7.98 (s, 1H), 10.72 (s, 1H).

3-(1-Methyl-3-phenyl-propyl)-3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (6d). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.60 (d, J = 6.8 Hz, 3H), 2.33

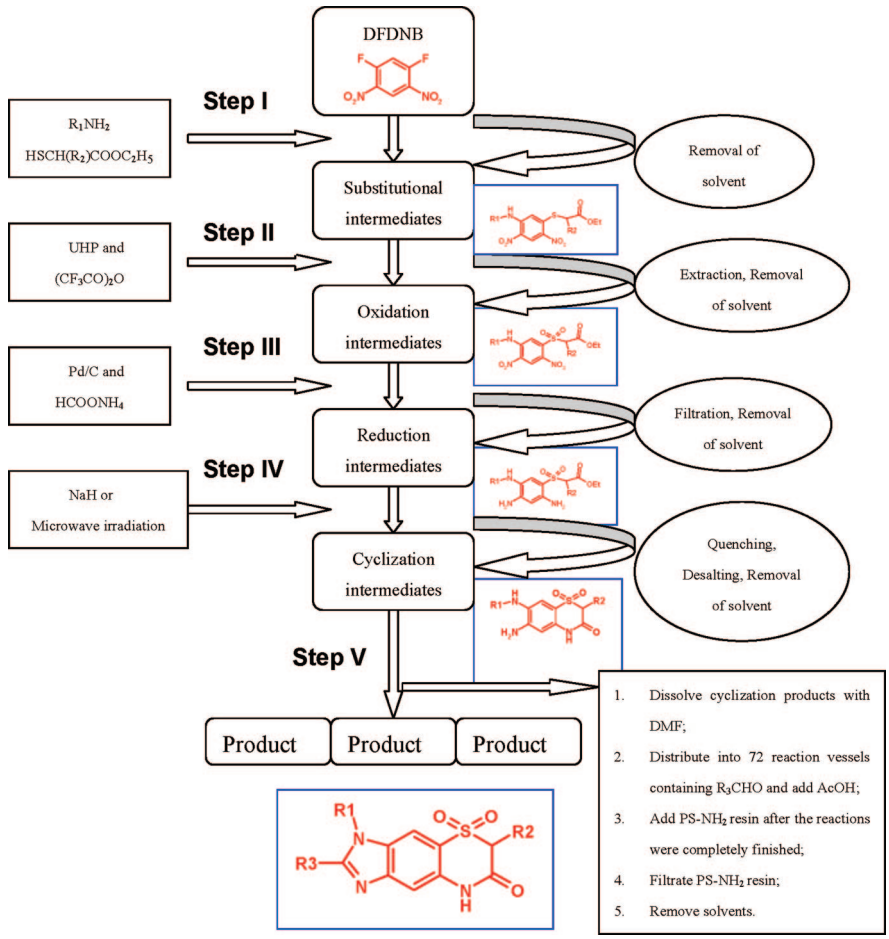


Figure 4. Flowchart for the preparation of scaffold **5** chemical library.

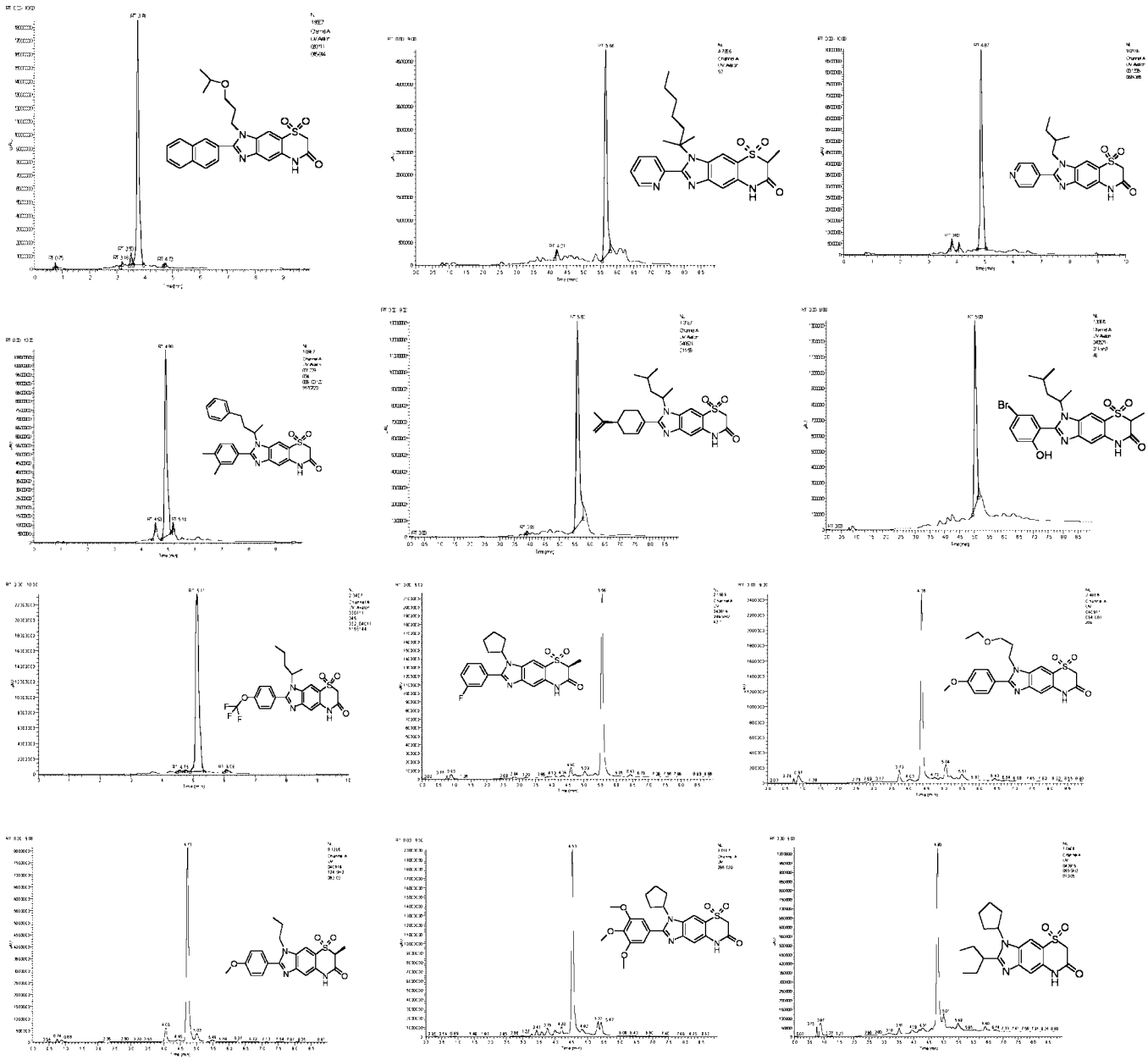


Figure 5. Typical compounds of scaffold **5** library.

(m, 4H), 3.55 (s, 2H), 5.01 (m, 1H), 7.08–7.25 (m, 5H), 7.52 (s, 1H), 7.93 (s, 1H), 10.72 (s, 1H).

3-(3,3-Diphenyl-propyl)-3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (6e). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.67 (m, 2H), 3.52 (s, 2H), 3.91 (t, J = 8.0 Hz, 1H), 4.52 (t, J = 7.2 Hz, 2H), 7.14–7.32 (m, 10H), 7.48 (s, 1H), 7.72 (s, 1H), 10.72 (s, 1H).

6-Methyl-3-phenethyl-3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (6f). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.32 (d, J = 7.2 Hz, 3H), 3.18 (t, J = 7.2 Hz, 2H), 3.72 (qu, J = 7.2 Hz, 1H), 4.88 (t, J = 7.2 Hz, 2H), 7.18 (m, 5H), 7.47 (s, 1H), 7.77 (s, 1H), 10.69 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 15.26, 35.29, 35.91, 48.84, 104.04, 109.12, 121.71, 126.54, 128.29, 128.84, 129.56, 134.08, 137.75, 144.21, 168.06.

6-Methyl-3-pentyl-3,8-dihydro-5-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (6g). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.82 (t, J = 7.2 Hz, 3H), 1.25 (m, 4H), 1.33 (d, J = 7.2 Hz, 3H), 1.95 (m, 2H), 3.76 (q, J = 7.2 Hz, 1H), 4.62 (m, 2H), 7.52 (s, 1H), 7.98 (s, 1H), 10.73 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 13.76, 15.16, 21.50, 28.14, 28.82, 35.87, 47.48, 104.18, 108.97, 121.96, 129.49, 134.22, 144.33, 168.08.

3-(1,1-Dimethyl-propyl)-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (7a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.60 (t, J = 7.2 Hz, 3H), 1.82 (s, 6H), 2.15 (qu, J = 6.8 Hz, 2H), 4.83 (s, 2H), 7.79 (s, 1H), 8.41 (s, 1H), 11.36 (s, 1H).

3-(1,1-Dimethyl-propyl)-6-methyl-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,2,3,8-tetraaza-cyclopenta[b]naphthalen-7-one (7b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.61 (t, J = 7.2 Hz, 3H), 1.49 (d, J = 7.6 Hz, 3H), 1.87 (s, 6H), 2.15 (qu, J = 7.2 Hz, 2H), 4.88 (qu, J = 7.2 Hz, 1H), 7.78 (s, 1H), 8.43 (s, 1H), 11.37 (s, 1H).

General Procedure for the Synthesis of Scaffold 8. To a solution of intermediate **2** (0.1 mmol) in anhydrous DCM

(5 mL) and Et_3N (0.1 mmol) was added dropwise a solution of triphosgene (0.1 mmol) in DCM (1 mL) under stirring at room temperature. The reaction was monitored by HPLC–MS analysis until the reaction was complete. Excess triphosgene was quenched by 2 mL of water, and then the mixture was extracted with DCM (10 mL × 2). The organic layer was combined and washed with saturated $NaHCO_3$ solution (10 mL × 2) and brine (10 mL × 2), and dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo*. The residue was finally purified on a silica gel column eluting with ethyl acetate and petroleum ether to give scaffold **8**. Typical compounds were characterized by NMR spectrometry and are listed below.

3-(1-Methyl-3-phenyl-propyl)-3,8-dihydro-1H-5-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (8a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.38 (d, J = 6.9 Hz, 3H), 2.00 (m, 2H), 2.36 (m, 2H), 3.38 (s, 2H), 4.34 (m, 1H), 6.67 (s, 1H), 7.11 (s, 1H), 7.13–7.22 (m, 5H), 10.37 (s, 1H), 10.81 (s, 1H).

6-Methyl-3-pentyl-3,8-dihydro-1H-5-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (8b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.82 (t, J = 7.2 Hz, 3H), 1.30 (d, J = 7.2 Hz, 3H), 1.25 (m, 4H), 1.57 (m, 2H), 3.55 (m, J = 7.2 Hz, 1H), 3.70 (t, J = 6.90 Hz, 2H), 6.67 (s, 1H), 7.08 (s, 1H), 10.36 (s, 1H), 10.79 (s, 1H).

6-Methyl-3-phenethyl-3,8-dihydro-1H-5-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (8c). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.27 (d, J = 6.9 Hz, 3H), 2.88 (t, J = 7.8 Hz, 2H), 3.52 (qu, J = 7.2 Hz, 1H), 3.94 (t, J = 7.8 Hz, 2H), 6.65 (s, 1H), 6.98 (s, 1H), 7.20 (m, 5H), 10.35 (s, 1H), 10.80 (s, 1H).

General Procedure for the Synthesis of Scaffold 9. Triphosgene (0.2 mmol) was added to a solution of intermediate **3** (0.1 mmol) in freshly distilled toluene (3 mL). The reaction mixture was irradiated under a CEM focused microwave synthesizer (W = 150 w, ramp time = 10 min, hold time = 60 min, P = 100 psi, T = 80 °C). The reaction was monitored by LC–MS analysis until it was complete. The reaction solution was evaporated *in vacuo* to dryness. The residue was purified on a silica gel column eluting with ethyl acetate and petroleum ether to give compounds **9**. Typical compounds were characterized by NMR spectrometry and are listed below.

3-(1,1-Dimethyl-propyl)-5,5-dioxo-3,5,6,8-tetrahydro-1H-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (9a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.73 (t, J = 7.6 Hz, 3H), 1.68 (s, 6H), 2.00 (qu, J = 8.0 Hz, 2H), 4.61 (s, 2H), 6.80 (s, 1H), 7.56 (s, 1H), 11.02 (s, 1H), 11.33 (s, 1H).

5,5-Dioxo-3-propyl-3,5,6,8-tetrahydro-1H-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (9b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.85 (t, J = 7.2 Hz, 3H), 1.62 (m, 2H), 3.80 (t, J = 7.2 Hz, 2H), 4.61 (s, 2H), 6.84 (s, 1H), 7.55 (s, 1H), 11.03 (s, 1H), 11.33 (s, 1H).

3-(3-Isopropoxy-propyl)-5,5-dioxo-3,5,6,8-tetrahydro-1H-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalene-2,7-dione (9c). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.04 (d, J = 6.0 Hz, 6H), 1.80 (m, 2H), 3.34 (m, 2H), 3.46 (m, 1H), 3.87 (t, J = 6.4 Hz, 2H), 4.59 (s, 2H), 6.83 (s, 1H), 7.50 (s, 1H), 11.03 (s, 1H), 11.33 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 21.91, 28.39, 37.61, 56.26, 64.11,70.67, 98.32, 101.55, 117.99, 126.71, 131.15, 133.52, 154.22, 161.96.

General Procedure for the Synthesis of Scaffold 10. Carbon disulfide (0.2 mmol) was added to a solution of intermediate **2** (0.1 mmol) and triethylamine (0.2 mmol) in 15 mL of anhydrous ethanol at room temperature. After the reaction was complete as monitored by HPLC–MS analysis, the solution was evaporated *in vacuo* to dryness. The residue was dissolved in DCM (15 mL), and then washed with saturated $NaHCO_3$ solution (10 mL × 2) and brine (10 mL × 2), and dried over anhydrous Na_2SO_4. After being dried over anhydrous Na_2SO_4, the filtrate was concentrated *in vacuo* to give crude **10**. The residue was purified on a silica gel column eluting with ethyl acetate and petroleum ether, and characterized by NMR spectrometry as listed below.

2-Mercapto-3-(2-methyl-benzyl)-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (10a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.38 (s, 3H), 3.41 (s,2H), 5.39 (s, 2H), 6.47 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 7.13 (s, 1H), 7.02–7.23 (m, 3H), 10.54 (s, 1H), 12.49 (s, 1H).

2-Mercapto-3-propyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (10b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.87 (t, J = 7.2 Hz, 3H), 1.68 (m, 2H), 3.44 (s, 2H), 4.10 (t, J = 7.2 Hz, 2H), 6.84 (s, 1H), 7.45 (s, 1H), 10.51 (s, 1H), 12.62 (s, 1H).

2-Mercapto-6-methyl-3-phenethyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (10c). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.28 (d, J = 7.2 Hz, 3H), 2.96 (t, J = 7.6 Hz, 2H), 3.58 (qu, J = 7.2 Hz, 1H), 4.35 (t, J = 7.6 Hz, 2H), 6.82 (s, 1H), 7.16 (s, 1H), 7.27 (m, 5H), 10.49 (s, 1H), 12.67 (s, 1H).

2-Mercapto-6-methyl-3-pentyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (10d). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.84 (t, J = 6.8 Hz, 3H), 1.29 (m, 7H), 1.66 (m, 2H), 3.63 (qu, J = 6.8 Hz, 1H), 4.14 (m, 2H), 6.85 (s, 1H), 7.41 (s, 1H), 10.50 (s, 1H), 12.62 (s, 1H).

General Procedure for the Synthesis of Scaffold 11. To a suspension mixture of K_2CO_3 (0.3 mmol) in 15 mL of anhydrous DMF was added intermediate **3** (0.1 mmol) at room temperature. The solution immediately turned from colorless to deep red and was kept stirring for 30 min at room temperature. Carbon disulfide was then quickly added. When the reaction was complete as monitored by HPLC–MS analysis, the mixture was diluted with water (2 mL) and extracted with EtOAc (10 mL × 2). The organic layer was combined and washed with saturated $NaHCO_3$ solution (20 mL × 3) and brine (20 mL × 2), and dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo*. The residue was purified on silica gel eluting with ethyl acetate and petroleum ether to give compounds **11**. Typical compounds were characterized by NMR spectrometry and the data are listed below.

2-Mercapto-6-methyl-5,5-dioxo-3-propyl-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (11a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.88 (t, J = 7.6 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.70 (m, 2H), 4.23 (m, 2H), 4.73 (qu, J = 7.2 Hz, 1H), 6.99 (s, 1H), 7.90 (s, 1H), 11.15 (s, 1H), 13.04 (s, 1H).

3-(1,1-Dimethyl-propyl)-2-mercapto-6-methyl-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (11b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.69 (t, J = 7.6 Hz, 3H), 1.43 (d, J = 6.8 Hz, 3H), 1.97 (s, 6H), 2.49 (m, 2H), 4.71 (qu, J = 7.2 Hz, 1H), 6.95 (s, 1H), 7.94 (s, 1H), 11.14 (s, 1H), 13.03 (s, 1H).

3-(1,1-Dimethyl-propyl)-2-mercapto-5,5-dioxo-3,5,6,8-tetrahydro-5λ^6-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (11c). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.69 (t, J = 7.6 Hz, 3H), 1.96 (s, 6H), 2.49 (qu, J = 7.6 Hz, 2H), 4.68 (s, 2H), 6.97 (s, 1H), 7.93 (s, 1H), 11.14 (s, 1H), 13.02 (s, 1H).

General Procedure for the Direct Synthesis of Compounds 12. Carbon disulfide (0.2 mmol) was added to a solution of intermediate **2** (0.1 mmol) and triethylamine (0.2 mmol) in 15 mL of anhydrous ethanol at room temperature. When the reaction was complete monitored by HPLC–MS analysis, the volatiles were evaporated *in vacuo* to dryness. Then alkyl bromide in 15 mL of anhydrous ethanol was added to the residue at room temperature. After compounds **10** converted completely to **12**, the solution was then evaporated *in vacuo* to dryness. The crude residue was redissolved in DCM (15 mL), washed with saturated $NaHCO_3$ solution (10 mL × 2) and brine (10 mL × 2), and dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* to give crude **12**, and the residue was purified on a silica gel column eluting with ethyl acetate and petroleum ether. Typical compounds were characterized by NMR spectrometry and the data are listed below.

2-Allylsulfanyl-3-propyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (12a). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.83 (t, J = 7.2 Hz, 3H), 1.68 (m, 2H), 3.45 (s, 2H), 3.98 (d, J = 6.8 Hz, 2H), 4.05 (t, J = 6.8 Hz, 2H), 5.10 (d, J = 10.0 Hz, 1H), 5.30 (d, J = 16.8 Hz, 1H), 5.98 (m, 1H), 7.15 (s, 1H), 7.54 (s, 1H), 10.45 (s, 1H).

2-Allylsulfanyl-3-(2-methyl-butyl)-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (12b). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.78 (d, J = 7.2 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H), 1.12–1.34 (m, 2H)· 1.90 (m, 1H), 3.43 (s, 2H), 3.86 (m, 2H), 3.97 (d, J = 6.4 Hz, 2H), 5.10 (d, J = 10.0 Hz, 1H), 5.28 (d, J = 16.8 Hz, 1H), 5.97 (m, 1H), 7.15 (s, 1H), 7.50 (s, 1H), 10.45 (s, 1H).

2-[2-(4-Methoxy-phenyl)-2-oxo-ethylsulfanyl]-6-methyl-3-pentyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (12c). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.84 (t, J = 6.8 Hz, 3H), 1.34 (m, 4H), 1.70 (m, 2H), 3.60 (qu, J = 6.8 Hz, 1H), 3.85 (s, 3H), 4.11 (t, J = 7.6 Hz, 2H), 4.99 (s, 2H), 7.06 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 8.02 (d, J = 8.8 Hz, 2H), 10.41 (s, 1H).

2-[2-(4-Methoxy-phenyl)-2-oxo-ethylsulfanyl]-6-methyl-3-phenethyl-3,8-dihydro-5-thia-1,3,8-triaza-cyclopenta[b]naphthalen-7-one (12d). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.28 (d, J = 7.2 Hz, 3H), 3.00 (t, J = 7.2 Hz, 2H), 3.57 (qu, J = 6.8 Hz, 1H), 3.85 (s, 3H), 4.34 (m, 2H), 4.94 (s, 2H), 7.04 (s, 1H), 7.05 (m, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.24 (m, 3H), 7.37 (s, 1H), 8.01 (d, J = 8.4 Hz, 2H), 10.39 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 15.05, 34.83, 36.19, 39.67, 45.30, 55.61, 105.01, 108.55, 112.93, 114.04, 126.58, 128.23, 128.34, 128.93, 130.80, 132.21, 132.30, 137.75, 141.75, 151.35, 163.54, 167.86, 191.46.

General Procedure for the Synthesis of Scaffold 5 Library from DFDNB. The library was synthesized on a scale of 0.05 mmol per compound. Intermediate **3** was prepared using our previously reported method.[11] Intermediate **3** (3.5 mmol) was dissolved in 70 mL of DMF containing 5% (v/v) AcOH and equally distributed into 70 reaction vessels of the H+P Labortechnik GmbH parallel synthesizer. Each reaction vessel was prelabeled by the corresponding aldehyde in Table 7. The aldehyde (3 equiv) was then added into the respective reaction vessel. The reaction mixtures were kept stirring at 55 °C. The reactions were monitored by HPLC–MS analysis. When the most difficult reaction did not progress, 500 mg of PS-NH_2 resin (4.3 equiv) was added to each reaction vessel and they were kept stirring for an additional 10 h to remove excess aldehydes. After parallel filtration with a special apparatus[17] and washing of resin by DMF, the organic solvent was removed under reduced pressure using an HT-4 series Genevac evaporator. The residues were redissolved in 4 mL of DCM/water (v/v = 1:1) and parallel separated using 15 mL of phase separators. The organic layer was collected and concentrated *in vacuo* to provide the final products. All the compounds were analyzed by HPLC–UV–ELSD or HPLC–UV–MS system.

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