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Facile Synthesis of Derivatives of 1,1,3-Trioxo-2*H*,4*H*-pyrrolo[1,2-*b*][1,2,4,6]thiatriazine: A New Heterocyclic System

Wenmin Chen, Peng Zhan, Diwakar Rai, Boshi Huang, Jiapei Yang, and Xinyong Liu

Department of Medicinal Chemistry, Key Laboratory of Chemical Biology of Natural Products (Ministry of Education), School of Pharmaceutical Sciences, Shandong University, 44, West Culture Road, 250012, Jinan, Shandong, People's Republic of China

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ABSTRACT: *We reported a facile and efficient methodology to synthesize derivatives of pyrrolo [1,2-b][1,2,4,6]thiatriazine (PTTD): a new bridgehead nitrogen heterocyclic system. Treatment of methyl pyrrole-2-carboxylate with N-benzylsulfamoyl chlorides followed by subsequent hydrolysis reaction afforded 1-benzylsulfamoyl-1H-pyrrole-2-carboxylic acids, which underwent ring-closing reaction by treatment with diphenyl phosphorazidate via Curtius rearrangement; subsequent alkylation reaction afforded the desired 2,4-disubstituted-1,1,3-trioxo-2H,4H-PTTDs.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem. 24:495–501, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21123

Correspondence to: Xinyong Liu; e-mail: xinyongl@sdu.edu.cn.
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INTRODUCTION

Heterocyclic compounds that constitute the largest important class of organic chemistry are significantly important in synthetic chemistry because of their broad pharmacological applications. Therefore, synthetic chemists have been engaged in extensive efforts to explore novel heterocyclic compounds with biological activities. Recently, there has been a great interest in heterothiadiazines because of their diverse antiviral activities against human cytomegalovirus, varicella zoster virus, hepatitis C virus, and human immunodeficiency virus (HIV) [1]. Among them, a class of 2,4-disubstitued-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazines (TTDs) (Fig. 1) was reported as potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) [2]. Structure-activity relationship studies of TTDs demonstrated that the dual substitutions at *N*-2 and *N*-4 positions of 1,2,4-TTD ring were necessary for their antiviral activities [3]. In an effort to explore bioisosteres of TTDs, we have synthesized three classes of heterothiadiazine derivatives: thieno[2,3-*e*][2,1,3]thiadiazines (TTDDs) [4], pyrazolo[4,5-*e*][2,1,3]thiadiazines (PTDDs) and pyrazolo[4,5-*e*][1,2,4]thiadiazines (PTDs) [5], which also displayed potential activities against HIV-1. As a continuation of our research, we constructed a new bridgehead nitrogen heterocyclic system, *viz*. 1,1,3-trioxo-2*H*,4*H*-pyrrolo[1,2-*b*][1,2,4,6]thiatriazine (PTTD) as the bioisostere of TTD (Fig. 1).

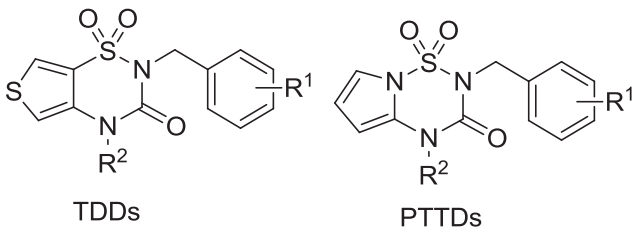


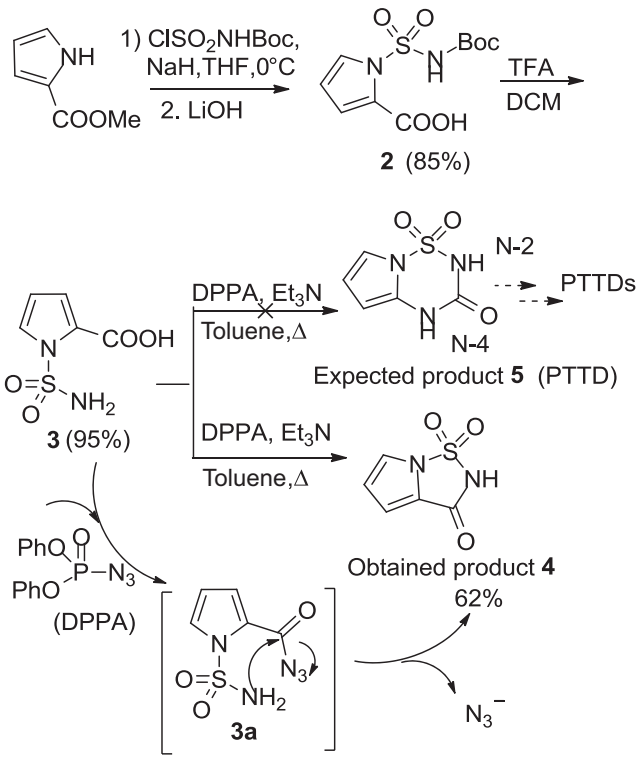
FIGURE 1 Structures of TTDs and PTTDs.

However, to the best of our knowledge, no synthetic method is yet available in the literature on this unique heterobicyclic ring system. In our previous studies, we have developed a methodology for preparing PTD by intramolecular cyclization of carboxylic acids with amino groups in the same molecules via Curtius rearrangement [5, 6]. It was envisioned that this methodology would allow for the synthesis of a range of a structurally diverse heterobicyclic ring system. So we decided to extend our method to synthesize PTTD. However, this classical Curtius reaction has considerable limitations, such as utilization of the toxic sodium azide or hydrazine as azide reagent [7] and isolation of potentially explosive acyl azide intermediates. Therefore, we decided to apply the safe diphenyl phosphorazidate (DPPA) [8] as the azide-transfer reagent. Herein, we report a facile and efficient methodology for the synthesis of 1,2,4,6-PTTDs, with convenient DPPA-modified Curtius reaction [9] as the key step.

RESULTS AND DISCUSSION

In our efforts to prepare the desired PTTD derivatives, two synthetic strategies were attempted. Inspired by the reported synthetic approach for PTD [10], our initial plan was to prepare a PTTD ring (**5**) which subsequently underwent regioselective *N*-alkylation at *N-2* and *N-4* positions, respectively, to give the target PTTDs (strategy 1, Scheme 1). The second strategy, which ultimately proved to be successful, was to join *N-2* benzyl group before the formation of PTTD ring (strategy 2, Scheme 2). The unsuccessful former approach will be discussed first, which shed light on some of the unique chemistry of PTTD (**5**).

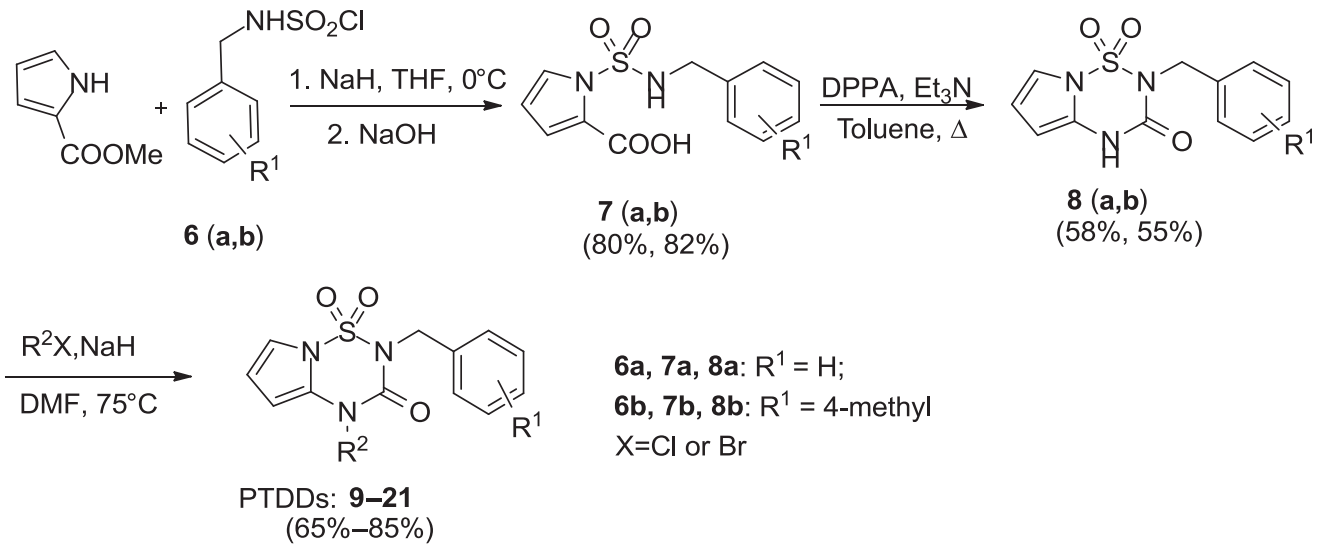
According to the first strategy, we first synthesized the key intermediate 1-(*N*-Boc-sulfamoyl)-1*H*-pyrrole-2-carboxylic acid (**2**) by treatment of methyl pyrrole-2-carboxylate with *N*-Boc-sulfamoyl chloride (**1**) in the presence of sodium hydride, followed by hydrolysis reaction in one pot in high yield (85%). Subsequently, treatment of **2** with DPPA generated no cyclization product. As an alternative approach to prepare PTTD ring, we then deprotected the *N*-Boc group of **2** utilizing trifluoroacetic acid to give sulfamoyl-1*H*-pyrrole-2-carboxylic acid (**3**, 95%), which would serve as a substrate for the Curtius reaction. However, the subsequent ring-closing reaction of **3** using DPPA and triethylamine in toluene at 65°C for 12 h led to the formation of 1,1,3-trioxo-2*H*-pyrrolo[1,2-*b*][1, 2, 5]thiadiazole (**4**) (yield 62%), rather than the expected PTTD ring (**5**) (Scheme 1).



SCHEME 1 Synthetic route of PTTDs by strategy 1.

We assumed that the acyl azide intermediate **3a** formed by the treatment of **3** with DPPA readily underwent an intramolecular nucleophilic attack of amino on the active carbonyl carbon to produce the cyclization product **4** without rearrangement (Scheme 1). The expected Curtius rearrangement reaction didn't occur even under higher temperature (80°C) and longer time (24 h). The nucleophilicity of sulfamoyl group and its favorable steric position for intramolecular reaction may be responsible for the high tendency of intramolecular nucleophilic reaction rather than rearrangement reaction in this case.

After the failure of the first synthetic strategy, we turned our attention to another alternative strategy, which was to join a steric *N-2* benzyl group before the formation of PTTD ring (Scheme 2, strategy 2). This synthetic strategy makes use of 1-benzylsulfamoyl-1*H*-pyrrole-2-carboxylic acids (**7a,b**) as the intermediate. The starting material



SCHEME 2 Synthetic route of PTTDs (**9–21**) by strategy 2.

N-benzylsulfamoyl chlorides **6** (**a**,**b**) were synthesized from commercially available benzylamines by the reported method [4]. The synthesis of 2-benzyl-1,1,3-trioxo-*2H,4H*-pyrrolo[1,2-*b*][1, 2, 4, 6]thiatriazine (**8a**) was taken as a model reaction. Methyl pyrrole-2-carboxylate (1.0 equivalent) was treated with **6a** (1.2 equiv) in the presence of excessive sodium hydride (3.0 equiv), followed by a subsequent hydrolysis reaction in one pot to provide 1-benzylsulfamoyl-1*H*-pyrrole-2-carboxylic acid **7a** in the yield of 82%. Subsequent ring-closing reaction of **7a** by treatment of DPPA (1.2 equiv) and triethylamine (1.2 equiv) via Curtius rearrangement at 70°C afforded **8a** in a yield of 58%.

The obtained (**8a**) was characterized by ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR, high resolution mass spectrometry (HRMS), and infrared (IR) spectroscopy, which support its structural features. One triplet at δ 6.42 and two double doublets at δ 5.66 and 7.13 in ^{1}H-NMR spectrum were attributable to the pyrrole protons. The carbonyl carbon (—C=O) signal at δ 147.9 and the N—H proton signal at δ 11.92 together with the corresponding infrared peaks at 3124 and 1707 cm^{-1} indicated the presence of —CONH— group in **8a**.

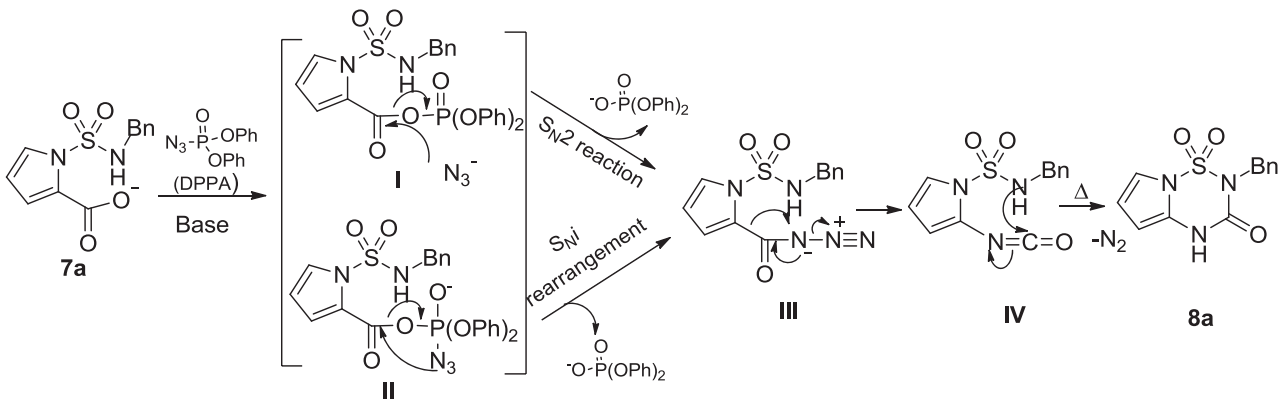
A plausible reaction mechanism for the synthesis of ring (**8a**) via ring-closing reaction using DPPA is depicted in Scheme 3 [9]. The carboxylate anion of **7a** attacked the phosphorus atom of DPPA and generated the acyl phosphates **I** and **II**, which respectively underwent S_N2-type reaction and S_Ni-type rearrangement with azide anion to form the acyl azide **III**. In the next step, the acyl azides **III** would thermally undergo the Curtius rearrangement to give the isocyanates **IV**. Then cyclization of intermediate **IV** was done via intramolecular electrophilic attack to form the heterobicyclic ring system **8a**. The steric hindrance of the internal benzylamine nucleophile in intermediate **IV** may limit the yields of pyrrolothiatriazines **8a** (58%).

With the optimized synthetic conditions in hand, 2-(4-methylbenzyl)-1,1,3-trioxo-*2H,4H*-pyrrolo[1,2-*b*][1,2,4,6]thiatriazine **8b** was also prepared according to the obtained synthetic route starting from 4-methylbenzylsulfamoyl chloride **6b** (Scheme 2).

After obtaining **8** (**a**,**b**), we further substituted at *N-4* position of PTTD ring with different benzyl, allyl, and alkyl halides or α-haloesters in the presence of sodium hydride to provide the desired PTTD compounds **9–21** (Scheme 2, Table 1). As shown in the Table 1, this method has the ability to tolerate a wide variety of substitutions in moderate to good yield (65%–85%). All the synthesized compounds were adequately characterized by the physical and spectral data.

CONCLUSIONS

In summary, we have developed a facile and efficient synthetic procedure for the preparation of derivatives of 1,2,4,6-PTTDs (**9–21**) using DPPA-mediated Curtius rearrangement as the key step. This modified Curtius reaction was performed using one-pot procedure without separating the explosive acyl azide intermedate; it was much simpler and less laborious than the classical Curtius reaction [8, 11]. Additionally, this new heterobicyclic ring system will serve as a new building block in medicinal and synthetic chemistry, and our further investigation on



SCHEME 3 A plausible reaction mechanism for the synthesis of **8a**.

TABLE 1 Synthesis of PTTDs (**9–21**)[a]

Entry	Substrate	R^2X	Product	Yield[b] (%)
1	**8a**	4-Chlorobenzyl chloride	**9**	82
2	**8a**	3-Bromobenzyl chloride	**10**	70
3	**8a**	3-Fluorobenzyl chloride	**11**	75
4	**8a**	Ethyl bromoacetate	**12**	82
5	**8a**	Methyl iodide	**13**	75
6	**8a**	Bromoethane	**14**	67
7	**8a**	4-Methylbenzyl chloride	**15**	75
8	**8a**	Cinnamyl chloride	**16**	78
9	**8a**	Allyl bromide	**17**	65
10	**8b**	4-Chlorobenzyl chloride	**18**	85
11	**8b**	3-Fluorobenzyl chloride	**19**	78
12	**8b**	4-Methyoxybenzyl chloride	**20**	72
13	**8b**	4-Methylbenzyl chloride	**21**	80

[a]Conditions: **8** (**a**,**b**) (1 mmol, 1.0 equiv), R^2X (1.2 mmol, 1.2 equiv), sodium hydride (60% in mineral oil, 1.2 mmol, 1.2 equiv), DMF (5 mL), 75°C, 12 h.
[b]Isolated yields after column chromatography.

the exploration of novel bioactive compounds containing PTTD scaffold is underway.

Experimental

Mass spectrometry was performed on an API 4000 triple-quadrupole mass spectrometer (Applied Biosystems/MDS Sciex, Concord, ON, Canada). IR spectra were recorded with Nicolet-6700 model FT-IR spectrometer (Thermo Scientific, Waltham, MA, USA) using KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 600 spectrometer (Bruker, Fällanden, Switzerland), Bruker AV-400 spectrometer (Bruker BioSpin, Switzerland), or Bruker AVANCE-300 spectrometer (Bruker BioSpin, Switzerland), using solvents as indicated ($CDCl_3$ or DMSO-d_6). Chemical shifts were reported in δ values (ppm) with tetramethylsilane as the internal reference, and J values were reported in hertz (Hz). Melting points (mp) were determined on a micromelting point apparatus (Tian Jin Analytical Instrument Factory, Nankai, Tianjin, China). Flash column chromatography was performed on columns packed with silica gel 60 (200–300 mesh) (Qingdao waves silica gel desiccant co., Ltd, Qingdao, China). Thin layer chromatography was performed on pre-coated HUANGHAI® HSGF254, 0.15-0.2 mm TLC-plates (Yantai Jiangyou Silica Gel Development Co., Ltd., Yantai, Shandong, China). Solvents (Tianjin Fuyu Fine Chemical Co., Ltd., Wuqing, Tianjin, China) were of reagent grade and were purified and dried by standard methods when necessary. The key reactants including methyl 1*H*-pyrrole-2-carboxylate, benzylamines, benzyl halides, alkyl halides, and DPPA were purchased from Adamas-beta Co. Ltd (Shanghai, China).

1-(N-Boc-sulfamoyl)-1H-pyrrole-2-carboxylic acid **2**. Methyl 1*H*-pyrrole-2-carboxylate (125 mg, 1.0 mmol, 1.0 equiv) was added to a stirring suspension of sodium hydride (60% in mineral oil) (80 mg, 2.0 mmol, 2.0 equiv) in 10 mL of anhydrous tetrahydrofuran (THF). The reaction mixture was stirred at 0°C for 30 min, and then a solution of *N*-Boc-sulfamoyl chloride (**1**) (1.5 mmol, 1.0 equiv, prepared in our lab) in anhydrous THF was dropwise added. After the completion of reaction, water was cautiously added to quench the reaction followed by the addition of 2N aq. LiOH solution (5 mL). The mixture solution was stirred at room temperature for 6 h. Then the organic solvent was removed under reduced pressure and the aqueous layer was acidified with concentrated hydrochloric acid to adjust to pH 1. The resulting precipitate was filtered off and subsequently purified by flash column chromatography to give the intermediate **2** as a white powder (85%), decomposed at 190–192°C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ ppm: 1.32 (s, 9H), 6.32

(t, $J = 3.0$ Hz, 1H), 7.07 (t, $J = 1.8$ Hz, 1H), 7.51 (s, 1H), 12.61 (s, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 27.87, 83.34, 109.71, 123.11, 125.30, 131.63, 149.37, 159.90; ESI-MS: 308.4 $[M+NH_4]^+$, 313.3 $[M+Na]^+$.

1-Sulfamoyl-1H-pyrrole-2-carboxylic acid **3**. 1-(*N*-Boc-sulfamoyl)-1*H*-pyrrole-2-carboxylic acid **2** (290 mg, 1.0 mmol, 1.0 equiv) and trifluoroacetic acid (1142 mg, 10 mmol, 10 equiv) was dissolved in 2 mL of dichloromethane, and stirred for 6 h at room temperature. Then the dichloromethane layer was removed under reduced pressure. The water was added to the remaining liquid and resulting precipitate was filtered off, and was purified by recrystallization using a mixture of petroleum ether and ethyl acetate to give intermediate **3** as a white powder (95%), decomposed at 194–196°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 6.25 (t, $J = 3.3$ Hz, 1H), 7.04 (dd, $J = 3.3$ Hz, 1.6 Hz, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 8.08 (s, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ ppm: 109.00, 122.37, 124.18, 128.82, 161.61; ESI-MS: 189.3 $[M-H]^-$; HRMS: $C_5H_5N_2O_4S$ $[M-H]^-$, found 188.9986, calcd 188.9976.

1,1,3-Trioxo-2H-pyrrolo[1,2-b][1,2,5]thiadiazole **4**. Triethylamine (12 mg, 1.2 mmol, 1.2 equiv) was added to a solution of intermediate **3** (190 mg, 1 mmol, 1.0 equiv) and DPPA (332 mg, 1.2 mmol, 1.2 equiv) in 100 mL of dry toluene. The reaction mixture was stirred at 70°C for 12 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using ethyl acetate/petroleum ether as eluent to yield 1,1,3-trioxo-2*H*-pyrrolo[1,2-*b*][1,2,5]thiadiazole (**4**) as a white powder (62%), decomposed at 198–200°C. ^{1}H-NMR (600 MHz, DMSO-d_6) δ ppm: 6.22 (s, 1H), 6.29 (s, 1H), 7.19 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 103.61, 116.14, 116.60, 134.34, 162.17; ESI-MS: 171.1 $[M-H]^-$; HRMS: $C_5H_3N_2O_3S$ $[M-H]^-$, found 170.9886, calcd 170.9870.

1-Benzylsulfamoyl-1H-pyrrole-2-carboxylic acid **7** *(***a,b***)*. Methyl pyrrole-2-carboxylate (125 mg, 1.0 mmol, 1.0 equiv) was added to a stirring suspension of sodium hydride (60% in mineral oil) (129 mg, 3.0 mmol, 3.0 equiv) in 5 mL of anhydrous THF. The reaction mixture was stirred at 0°C for 30 min, and then a solution of *N*-benzylsulfamoyl chloride (**6a**) (2 mmol, 2.0 equiv, prepared in our lab) in anhydrous THF was dropwise added. After completion of the reaction, water was cautiously added to quench the reaction followed by the addition of 2 mL of 5N aq. NaOH solution. The mixture solution was stirred at room temperature for 12 h. Then the organic solvent was removed under reduced pressure and the remaining aqueous solution was acidified with concentrated hydrochloric acid to adjust to pH 1. The resulting precipitate was filtered off and purified by column chromatography using ethyl acetate/petroleum ether as eluent to give intermediate **7a** as a white solid (82%): mp: 124–126°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm: 4.21 (s, 2H, CH_2), 6.18 (t, $J = 3.3$ Hz, 1H), 6.92 (dd, $J = 3.6$ Hz, $J = 1.8$ Hz, 1H), 7.17–7.25 (m, 5H), 7.32 (dd, $J = 3.0$ Hz, 1.8 Hz, 1H), 8.31 (s, 1H, NH), 12.84 (brs, 1H, OH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ ppm: 47.5, 161.2, 109.4, 122.6, 122.4, 127.9, 128.1, 128.7, 129.7, 136.7; ESI-MS: 281.5 $[M+H]^+$, 303.5 $[M+Na]^+$, 298.7 $[M+NH_4]^+$.

1-(4-methylbenzyl)sulfamoyl-1*H*-pyrrole-2-carboxylic acid (**7b**): White solid (80% yield): mp: 135–137°C; ESI-MS: 295.2 $[M+H]^+$.

General procedure for the preparation of 2-benzyl-1,1,3-trioxo-2H,4H-pyrrolo[1,2-b][1,2,4,6]thiatriazines **8** *(***a,b***)*. Triethylamine (121 mg, 1.2 mmol, 1.2 equiv) was added to a solution of **7(a,b)** (1.0 mmol, 1.0 equiv) and DPPA (332 mg, 1.2 mmol, 1.0 equiv) in 100 mL of dry toluene. The reaction mixture was stirred at 70°C for 12 h. The solvent was evaporated and the residue was purified by flash column chromatography using ethyl acetate/petroleum ether as eluent to yield **8** (**a,b**).

2-Benzyl-1,1,3-trioxo-2H,4H-pyrrolo[1,2-b][1,2,4,6]thiatriazine **8a**. White solid (58%): mp: 128–130°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm: 5.02 (s, 2H), 5.66 (dd, $J = 3.6$ Hz, 1.5 Hz, 1H), 6.42 (t, $J = 3.4$ Hz, 1H), 7.13 (dd, $J = 3.3$ Hz, 1.5 Hz, 1H), 7.27–7.38 (m, 5H), 11.92 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ ppm: 45.90, 93.25, 110.82, 114.43, 136.35, 128.34, 128.85, 128.42, 129.01, 147.92; ESI-MS: 278.3 $[M+H]^+$; HRMS: $C_{12}H_{12}N_3O_3S$ $[M+H]^+$, found 278.0437, calcd 278.0594.

2-(4-Methylbenzyl)-1,1,3-trioxo-2H,4H-pyrrolo[1,2-b][1,2,4,6]thiatriazine **8b**. White solid (55% yield): mp: 120–122°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.50 (s, 3H), 4.97 (s, 2H), 5.65 (dd, $J = 3.4$ Hz, 1.5 Hz, 1H), 6.40 (t, $J = 3.4$ Hz, 1H), 7.11 (dd, $J = 3.4$ Hz, 1.6 Hz, 1H), 7.13–7.26 (m, 5H), 11.85 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 45.80, 93.10, 110.70, 114.36, 128.17, 128.40 (2C), 129.21, 129.55 (2C), 133.26, 137.69, 147.89; ESI-MS: 291.3 $[M+H]^+$; HRMS: $C_{13}H_{14}N_3O_3S$ $[M+H]^+$, found 292.0658, calcd 292.0750.

General procedure for the preparation of 2,4-disubstitued-1,1,3-trioxo-2H,4H-pyrrolo[1,2-b][1,2,4,6]thiatriazines **9–21** *(Scheme 2, Table 1)*. Sodium

hydride (57.6 mg, 2.4 mmol) was added to a solution of **8** (**a,b**) (2.0 mmol) in dry DMF (10 mL) at 0°C. After stirring for 15 min, the corresponding alkyl halide (2.4 mmol) was added. The resulting mixture was stirred at 75°C for 12 h. Then the solvent was evaporated in vacuum and the residue was purified by flash column chromatography using dichloromethane/petroleum ether as an eluent to give **9–21**.

Compound 9 (Table 1, entry 1). Colorless crystal (82% yield): mp: 99–100°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 5.01 (s, 2H), 5.11 (s, 2H), 5.52 (dd, J = 3.4 Hz, 1.2 Hz, 1H), 6.27 (t, J = 3.4 Hz, 1H), 6.91 (dd, J = 3.2 Hz, 1.2 Hz, 1H), 7.16 (m, 2H), 7.25–7.37 (m, 5H), 7.47 (d, J = 6.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 47.30, 49.08, 94.76, 111.20, 113.20, 128.22, 128.44, 128.72, 128.78, 129.09, 129.68, 133.42, 133.84, 135.02, 148.64; ESI-MS: 402.5 $[M+H]^+$.

Compound 10 (Table 1, entry 2). White solid (70% yield): mp: 102–103°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 4.98 (s, 2H), 5.10 (s, 2H), 5.57 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.26 (t, J = 3.5 Hz, 1H), 6.82 (dd, J = 6.7 Hz, 2.0 Hz, 2H), 6.89 (dd, J = 3.4 Hz, 1.6 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.30–7.37 (m, 3H), 7.47 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 47.29, 49.06, 94.76, 111.23, 113.25, 122.95, 125.28, 128.44, 128.73 (4C), 129.60, 129.90, 130.48, 131.15, 134.97, 137.21, 148.61; ESI-MS: 446.4 $[M+H]^+$, 448.3 $[M+H]^+$, 468.2 $[M+Na]^+$, 470.3 $[M+Na]^+$.

Compound 11 (Table 1, entry 3). White solid (75% yield): mp: 89–90°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 5.04 (s, 2H), 5.12 (s, 2H), 5.52 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.27 (t, J = 3.4 Hz, 1H), 6.92–7.02 (m, 4H), 7.26–7.37 (m, 4H), 7.47 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 47.33, 49.21 (d, J = 1.7 Hz), 94.76, 111.21, 113.23, 113.88 (d, J = 22.3 Hz), 151.66 (d, J = 21.0 Hz), 122.34 (d, J = 3.0 Hz), 128.45, 128.73 (2C), 128.77 (2C), 129.70, 130.51 (d, J = 8.3 Hz), 135.01, 137.45, (d, J = 7.1 Hz), 148.65, 163.08 (d, J = 245.8 Hz); ESI-MS: 386.5 $[M+H]^+$, 408.4 $[M+Na]^+$.

Compound 12 (Table 1, entry 4). White solid (82% yield): mp: 85–86°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 1.23 (t, J = 7.1 Hz, 3H), 4.21 (q, J = 7.1 Hz, 2H), 4.51 (s, 2H), 5.08 (s, 2H), 5.54 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.32 (t, J = 3.5 Hz, 1H,), 6.93 (dd, J = 3.4 Hz, 1.6 Hz, 1H), 7.25–7.36 (m, 3H), 7.45–7.47 (m, 2H); ^{3}C-NMR (100 MHz, $CDCl_3$): 47.15, 49.32, 55.26, 94.80, 110.94, 113.22, 114.26, 126.97, 128.35 (2C), 128.73 (2C), 129.92, 135.17, 148.63, 159.31; ESI-MS: 364.4 $[M+H]^+$, 386.5 $[M+Na]^+$.

Compound 13 (Table 1, entry 5). White solid (75% yield): mp: 122–123°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 3.37 (s, 3H), 5.06 (s, 2H), 5.63 (dd, J = 3.4 Hz, 1.5 Hz, 1H), 6.35 (t, J = 3.5 Hz, 1H), 6.92 (dd, J = 3.3 Hz, 1.5 Hz, 1H), 7.21–7.37 (m, 3H), 7.47 (d, J = 6.7 Hz, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ ppm: 32.82, 46.94, 93.48, 111.09, 113.20, 128.34, 128.65 (2C), 128.82 (2C), 130.71, 135.12, 148.26; ESI-MS: 292.4 $[M+H]^+$, 314.4 $[M+Na]^+$.

Compound 14 (Table 1, entry 6). White solid (67% yield): mp: 94–97°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 1.31 (t, J = 7.1 Hz, 3H), 3.90 (q, J = 7.1 Hz, 2H), 5.06 (s, 2H), 5.66 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 6.36 (t, J = 3.5 Hz, 1H), 6.92 (dd, J = 3.4 Hz, 1.6 Hz, 1H), 7.25–7.36 (m, 3H), 7.43–7.45 (d, J = 6.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 14.03, 47.35, 62.03, 93.46, 111.36, 113.11, 128.38 (2C), 128.68 (2C), 129.84, 134.90, 148.51, 166.71; ESI-MS: 306.4 $[M+H]^+$.

Compound 15 (Table 1, entry 7). White solid (75% yield): mp: 86–88°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.3 (s, 3H), 5.00 (s, 2H), 5.11 (s, 2H), 5.55 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 6.25 (t, J = 3.5 Hz, 1H), 6.89 (dd, J = 3.4 Hz, 1.5 Hz, 1 H), 7.09–7.14 (m, 4H), 7.30–7.36 (m, 3H), 7.47 (d, J = 2.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 21.09, 47.16, 49.57, 94.81, 110.94, 113.24, 126.83, 128.34, 128.69, 128.77, 129.53, 129.94, 131.89, 135.174, 148.64; ESI-MS: 382.5 $[M+H]^+$, 404.5 $[M+Na]^+$.

Compound 16 (Table 1, entry 8). Colorless oil (78% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 4.61 (dd, J = 6.0 Hz, 1.4 Hz, 2H), 5.09 (s, 2H), 5.72 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.18–6.23 (m, 1H), 6.33 (t, J = 3.4 Hz, 1H), 6.61 (d, J = 1.6 Hz, 1H), 6.93 (dd, J = 3.4 Hz, 1.6 Hz, 1H), 7.25–7.34 (m, 8H), 7.34 (d, J = 1.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 47.12, 48.52, 94.28, 110.99, 113.30, 121.73, 126.60 (2C), 128.16, 128.40, 128.63 (2C), 128.72 (2C), 128.85 (2C), 129.88, 133.89, 135.13, 135.88, 148.14; ESI-MS: 394.5 $[M+H]^+$, 411.4 $[M+NH_4]^+$, 416.5 $[M+Na]^+$.

Compound 17 (Table 1, entry 9). White solid (65% yield): mp: 80–82°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 4.45 (d, J = 5.4 Hz, 1H), 5.07 (s, 2H), 5.24–5.28 (m, 2H), 5.65 (dd, J = 3.4 Hz, 1.4 Hz, 1H), 5.79–5.89 (m, 1H), 6.33 (t, J = 3.5 Hz, 1H), 6.92 (dd, J = 3.4 Hz, 1.5 Hz, 1H), 7.28–7.34 (m, 3H), 7.36 (d, J = 2.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 47.06, 48.71, 94.21, 110.95, 113.20, 118.36, 128.34, 128.67 (2C), 128.79 (2C), 129.87, 130.50, 135.13, 148.08; ESI-MS: 318.5 $[M+H]^+$, 340.5 $[M+Na]^+$.

Compound 18 (Table 1, entry 10). White solid (85% yield): mp: 95–98°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.34 (s, 3H), 5.00 (s, 2H), 5.07 (s, 2H), 5.51 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 6.26 (t, J = 3.4 Hz, 1H), 6.90 (dd, J = 3.4 Hz, 1.4 Hz, 1H), 7.14–7.17 (m, 4H), 7.25–7.29 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 21.22, 47.16, 49.04, 94.68, 111.14, 113.14, 128.22 (2C), 128.87 (2C), 129.08 (2C), 129.41 (2C), 132.02, 133.45, 133.80, 138.31, 148.65; ESI-MS: 416.4 $[M+H]^+$, 418.5 $[M+H]^+$, 433.5 $[M+NH_4]^+$, 438.4 $[M+Na]^+$, 440.5 $[M+Na]^+$.

Compound 19 (Table 1, entry 11). White solid (78% yield): mp: 88–90°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.32 (s, 3H), 5.03 (s, 2H), 5.08 (s, 2H), 5.51 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 6.26 (t, J = 3.5 Hz, 1H), 6.90 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 6.94–7.01 (m, 3H), 7.15 (d, J = 7.9 Hz, 2H), 7.25–7.28 (m, 1H), 7.37 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 21.18, 47.24, 49.21 (d, J = 1.8 Hz), 94.67, 111.18, 113.16, 113.89 (d, J = 21.3 Hz), 114.91 (d, J = 21.1 Hz), 122.34 (d, J = 2.9 Hz), 128.85, 129.42 (2C), 129.77 (2C), 130.50 (d, J = 8.1 Hz), 132.06, 137.53 (d, J = 7.3 Hz), 138.31, 148.70, 163.11 (d, J = 245.5 Hz); ESI-MS: 400.3 $[M+H]^+$, 417.5 $[M+NH_4]^+$, 422.4 $[M+Na]^+$.

Compound 20 (Table 1, entry 12). White solid (72% yield): mp: 98–100°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.33 (s, 3H), 3.76 (s, 3H), 4.98 (s, 2H), 5.07 (s, 2H), 5.56 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 6.25 (t, J = 3.5 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.88 (dd, J = 3.4 Hz, 1.5 Hz, 1H), 7.14–7.18 (m, 4H), 7.37 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 21.19, 47.05, 49.32, 55.28, 94.73, 110.91, 113.51, 114.29 (2C), 127.05, 128.36 (2C), 128.85 (2C), 129.37 (2C), 129.98, 132.22, 138.18, 148.69, 159.34; ESI-MS: 412.5 $[M+H]^+$, 429.5 $[M+NH_4]^+$, 434.5 $[M+Na]^+$.

Compound 21 (Table 1, entry 13). White solid (80% yield): mp: 92–94°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 2.31 (s, 3H), 2.34 (s, 3H), 5.01 (s, 2H), 5.08 (s, 2H), 5.54 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 6.25 (t, J = 3.5 Hz, 1H), 6.88 (dd, J = 3.4 Hz, 1.5 Hz, 1H), 7.07–7.16 (m, 6H), 7.37 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 21.11, 21.21, 47.02, 49.52, 94.74, 110.88, 113.18, 126.83 (2C), 128.86 (2C), 129.37 (2C), 129.53 (2C), 129.93, 131.91, 132.18, 148.66; ESI-MS: 396.3 $[M+H]^+$, 418.5 $[M+Na]^+$.

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