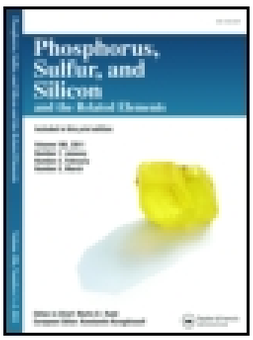

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Design, synthesis, and toward a side-ring optimization of tricyclic thieno[2,3-*d*]pyrimidin-4(3*H*)-ones and their effect on melanin synthesis in murine B16 cells

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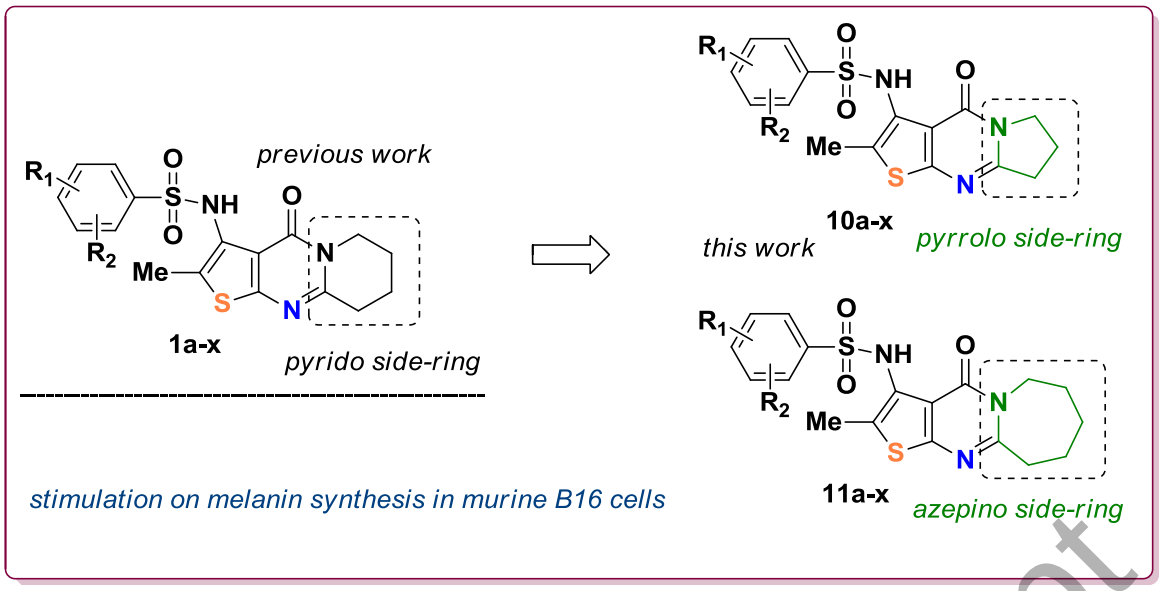
ABSTRACT

Herein, we report the synthesis of forty-eight novel 3-sulfonylamides containing a tricyclic thieno[2,3-*d*]pyrimidin-4(3*H*)-one moiety, and their influence on melanin synthesis in murine B16 cells. All target sulfonylamides were synthesized through key intermediate 3-nitro-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones using three types of *ipso*-nitration reactions. In this case, we converted the pyrido[1,2-*a*]- fragment of the thieno[2,3-*d*]pyrimidine moiety to pyrrolo[1,2-*a*]- and azepino[1,2-*a*]- side-rings in order to evaluate the bioactivities of the synthesized derivatives for a structure activity-relationships point of view. The obtained results suggest that some of the selected compounds revealed a promising influence on melanin synthesis in murine B16 cells and may serve as lead compounds for further drug discovery and development.

Graphic Abstract



Keywords: Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones; sulfonylamides; *ipso*-nitration; melanin synthesis; murine B16 cells

Introduction

Human skin cancer types - such as cutaneous malignant melanoma (melanoma), basal cell and squamous cell carcinomas of the skin (non-melanoma skin cancer) are now the most common types of cancer in populations all over the world, and the incidence of skin cancer has reached epidemic proportions.[1, 2] In humans, melanin production is important for the prevention of skin cancers, such as melanoma. Melanogenesis[3, 4] is a multistage process involving melanin synthesis, melanin transport, and melanosome release. Additionally, melanin synthesis is stimulated by various effectors, including α-melanocyte-stimulating hormone[5] (α-MSH), theophylline, cyclic AMP (cAMP)-elevating agents, and ultraviolet light.[6] Thus, skin pigmentation is the result of melanogenesis that occurs in melanocytes and/or melanoma cells. Although melanogenesis is necessary for the prevention of DNA damage and cancer caused by UV irradiation, excessive accumulation of melanin can also cause melanoma.[7] It is known that natural products are a good arsenal for treatment of the cancer-related diseases;[8, 9] however heterocyclic synthetic compounds also provide a special role in medicinal chemistry.[10, 11] Therefore, treatment of skin cancer, melanoma or vitiligo on the basis of heterocyclic compounds is becoming important approach in drug discovery.

It is known that structurally similar compounds do have similar biological activity.[12] Recently, we have reported[13] novel pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine derivatives **1a-x** (Chart 1) based on their structural similarities with 8-methoxyposralen (8-MOP, a drug-candidate for vitiligo treatment). The best results on melanin synthesis in murine B16 cells revealed that further structural optimization could be perspective. Likewise, because of their excellent opportunities

thieno[2,3-*d*]pyrimidines (Fig. 1) have become attractive to researchers studying multiple aspects of medicinal chemistry,[14-19] in particular for their anticancer properties.[20]

<Figure 1>

Thus, continuing our systematic research, herein we present a cycloalkane side-ring optimization of 3-sulfonylamide containing tricyclic thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **10a-x** and **11a-x** (Chart 1) and their influence on melanin synthesis in murine B16 cells.

<Chart 1>

Results and discussion

Synthesis

General synthetic routes of the target thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**10a-x** and **11a-x**) are described in Scheme 1. 2,3-Dimethyl pyrrolo[1,2-*a*]- (**2**) and azepino[1,2-*a*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**3**) derivatives were selected as starting materials and obtained by the condensation of 2-amino-4,5-dimethyl-3-carboxylate with appropriate lactams using phosphorus oxychloride.[21, 22] If derivatives **2** and **3** interact with concentrated HNO_3/H_2SO_4, unexpected oxidation of the methyl substituent at position 3 was observed, which gave selective 3-carboxy thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**4** and **5**).[23] Selective nitro products **6** and **7** were synthesized from derivatives **4** and **5** using $Cu(OAc)_2$ and $AgNO_3$ as nitrate sources. An intermediates **6** and **7** were subjected to the recovery reaction using $SnCl_2 \cdot 2H_2O$, and afforded amino derivatives **8** and **9**. Thus, the target sulfonylamides were synthesized from the target intermediates **8** and **9** and appropriate benzensulfonyl chlorides, using dichloromethane as the solvent.

<Scheme 1>

We decided that 3-nitro derivatives (**6** and **7**) are key intermediates for the synthesis of the target compounds. Therefore, we tried to optimize and suggest more appropriate pathways *via* *ipso*-nitration reactions.[24] The methyl 2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-3-carboxylate can be functionalized by the esterification reaction from acid **4**. Treatment of the methyl 2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidine-3-carboxylate with HNO_3/H_2SO_4 gave the selective 3-nitro product **6**. (Pathway 1, Scheme 2). In addition, this reaction demonstrates that *ipso*-nitration of the ester substituents are possible without metal-catalyzed assistance.

<Scheme 2>

Quinolone bearing acids were converted to selective nitro products using various nitrate sources, Lewis acids and metal salts.[25] In our case, thieno[2,3-*d*]pyrimidin-4(3*H*)-one moiety has π-excess electrons, therefore the reactivity of the thieno[2,3-*d*]pyrimidin-4(3*H*)-ones are higher than quinolones in the *ipso*-nitration reactions. In order to convert 3-carboxy thieno[2,3-

d]pyrimidin-4(3*H*)-one to 3-nitro thieno[2,3-*d*]pyrimidin-4(3*H*)-one (Pathway 2, Table 1), we have selected derivative **4** as the starting material, copper(II) acetate as Lewis acid (in a ratio of 50, 70 and 100 mol%), and metal salts such as $AgNO_3$, $NaNO_3$, $Ca(NO_3)_2$ as nitrating agents for the *ipso*-nitration reaction. The best results were obtained with $AgNO_3$, (herein $Cu(OAc)_2$ = 70 mol%; temperature = 80°C; solvent = ethanol), and were suggested as the method of choice for synthesis of corresponding 3-nitro thieno[2,3-d]pyrimidin-4(3H)-ones (Table 1, entry 4).

<Table 1>

If substrate **2** interacts with HNO_3/H_2SO_4, no selective nitro product was formed (Table 2). Nitrating mixtures HNO_3/CH_3COOH and $HNO_3/(CH_3CO)_2O$ resulted very less yields (5 %), while with $Cu(NO_3)_2/(CH_3CO)_2O$ mixture we have observed only trace of selective nitro product **6**. However, when HNO_3 and substrate **2** interacted at -25 – 10 °C for 2 h, derivative **6** was obtained in 15 % (Table 2, entry 5) (Pathway 3).

<Table 2>

Melanin synthesis evaluation in B16 cells

Previous screening[13,26] revealed that pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidinone demonstrated promising activity on melanin synthesis in murine B16 cells and may serve as lead compounds for further drug discovery and treatment of vitiligo. Likewise, present results showed that among the derivatives of pyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidinone, several compounds (**10k**, 329%; **10n**, 367%; **10x**, 329%) exhibited the best potency (Fig. S 2, Supplemental Materials). After side-ring optimization (from pyrido- to pyrrolo- side-ring), substituents at the *p*-position showed higher percentages on the melanin synthesis potency. For example, compound **10m** (with *p*- trifluoromethyl substituent) was more effective than compounds **10i** (with *o*-trifluoromethyl substituent) and **10j** (with *m*- trifluoromethyl substituent) on melanin synthesis evaluation in B16 cells. A similar case was observed among compounds with trifluromethoxy group (**10l-10n**) substitution.

In case of the azepino[1,2-*a*]thieno[2,3-*d*]pyrimidinones, di-fluoro- substituents impacted better activity. For example, derivative with 3,5-difluoro- substituent (**11o**, 369%) showed a better activity than other difluoro derivatives **11p-11s**. Conversely, the replacement of both fluorine of **11o** with chlorine dramatically decreased the activity (**11w**, 220%). The introduction of methyl substituent (compound **11t**, 400%), instead of inactive derivative with *p*-fluorine substituent (**11p**, 75%), increased the activity by 5.3-fold. Results are summarized in Figure S 2 (Supplemental Materials).

Experimental

Chemistry

Materials and methods. Reagents and solvents were purchased from Sigma, and used without further purification. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 200–300 mesh). Melting points were determined on a Buchi B-540 apparatus and uncorrected. All the NMR spectra were recorded with a Varian 400 MHz NMR spectrometer in $CDCl_3$, using TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded on AB SCIEX QSTAR Elite quadrupole time-of-flight mass spectrometry.

General procedure of preparation of 4 and 5. To cooled $H_2SO_{4(conc.)}$ (7.5 mL) was added compound **2** or **3** (42.73 mmol) at -10-15 °C. Next, a nitrating mixture (14.9 mL HNO_3 and 14 mL H_2SO_4) was added drop wise for 30 min. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with chloroform (2×100 mL). The organic layer was washed with water, and dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography to afford products **4** and **5**.

2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidine-3-carboxylic acid (4). Yield 92%, white solid, mp 257-259 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (t, *J* = 7.6 Hz, 2H), 3.25 (t, *J* = 8.0 Hz, 2H), 2.90 (s, 3H), 2.46 – 2.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.38, 162.31, 159.68, 159.58, 151.91, 122.53, 118.27, 47.45, 31.84, 19.66, 17.34. HRMS (ESI) calcd for $C_{11}H_9N_2O_3S$ $[M-H]^-$ 249.0334, found 249.0339.

2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxylic acid (5). Yield 91%, white solid, mp 247-249 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (t, *J* =6.8 Hz, 2H), 3.11 (t, *J* = 7.1 Hz, 2H), 2.90 (s, 3H), 1.98 – 1.74 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.45, 161.50, 160.73, 159.72, 152.12, 122.81, 118.18, 43.92, 37.06, 29.30, 27.23, 24.86, 17.41. HRMS (ESI) calcd for $C_{13}H_{13}N_2O_3S$ $[M-H]^-$ 277.0646, found 277.0652.

General procedure of preparation of 6 and 7. Compounds **6** and **7** were synthesized by a previously reported methodology.[23] Briefly, to a mixture of thieno[2,3-d]pyrimidin-4-one acids (**4** and **5**, 1 mmol), copper(II)acetate (70 mol%) and $AgNO_3$ (1.2 mmol) was added ethanol (10 mL) and the reaction mixture was refluxed during 10 h. The reaction mixture was cooled and diluted with EtOAc (3×10 mL). The organic layer was washed with an aqueous solution of saturated $NaHCO_3$, water, brine, and dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography to afford selective nitro products **6** and **7.** The Supplemental Materials contains sample 1H and 13C NMR spectra for the products 10 and 11 (Figures S 3 – S 88).

General procedure of preparation of 8 and 9. Into a three-necked flask added $SnCl_2 \cdot 2H_2O$ (102 mmol), conc. HCl (31 mL, 36%) and was stirred 5 min. Next, added a suspension of **6** or **7** (34 mmol) (EtOH 48 mL and conc. HCl (16 mL), and stirred for another 10–15 min in ice bath.

Stirring was continued at room temperature (0.5 h). The reaction was continued with vigorous stirring on a boiling water bath for 2 h. The mixture was diluted with water, and neutralized with NaOH solution (10%) until the pH was 11. The resulting precipitate was filtered off, washed with distilled water, dried and purified by silica gel chromatography to produce the pure corresponding compounds (**8** and **9**).

3-Amino-2-methyl-7,8-dihydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-4(6H)-one (8). Yield 92%, white solid, mp 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16(s, 2H), 3.98(t, *J* = 7.5 Hz, 2H), 3.02 (t, *J* = 7.8 Hz, 2H), 2.15 (s, 3H), 1.98 – 1.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.46, 159.77, 157.60, 136.99, 113.43, 101.25, 45.86, 31.42, 19.12, 10.88. HRMS (ESI) calcd for $C_{10}H_{11}N_3OS$ $[M-H]^-$ 221.0618, found 221.0623.

3-Amino-2-methyl-7,8,9,10-tetrahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-4(6H)-one (9). Yield 91%, white solid, mp 184-186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ5.21(s, 2H), 4.21(t, *J* = 7.8 Hz, 2H), 3.18 (t, *J* = 8.0 Hz, 2H), 2.75 (s, 3H), 1.98 – 1.74 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.67, 160.34, 159.17, 137.52, 119.84, 108.67, 42.32, 36.91, 29.36, 26.73, 21.48, 15.611. HRMS (ESI) calcd for $C_{12}H_{15}N_3OS$ $[M-H]^-$ 249.0931, found 249.0936.

General procedure of preparation of 10a-x and 11a-x. To a mixture of 3-amino-2-methyl-thieno[2,3-d]pyrimidin-4(6H)-one (1.0 mmol) (**8** and **9**) and benzenesulfonyl chloride (1.1 mmol) in DCM (10 mL) was added dropwise pyridine (1.2 mmol) in dichloromethane (2 mL). The resulting mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure, and the residue was treated with water (30 mL). The aqueous mixture was neutralized by the addition of aqueous 10% HCl solution and extracted with DCM (2 x 30 mL). The organic phase was washed with aqueous saturated NH_4Cl solution and brine. The organic layer was separated and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography to produce the pure corresponding compounds.

N-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10a). Yield 92%, light yellow solid, mp 149-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 3H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 2H), 3.89 (t, *J* = 7.4 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.61 (s, 3H), 2.25 – 2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.79, 159.73, 156.76, 138.45, 132.63, 131.48, 128.30, 127.87, 124.75, 115.81, 45.95, 31.99, 19.57, 13.86. IR (KBr) *v*: 2920, 1668, 1543, 1444, 1171, 1086, 751 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{15}N_3O_3S_2$ $[M-H]^-$ 361.0565., found 361.0555.

4-Methyl-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10b). Yield 87%, light yellow solid, mp 141-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.58 – 7.47 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 3.92 (t, *J* = 7.3 Hz, 2H), 3.07 (t, *J* = 7.9 Hz, 2H), 2.64 – 2.54 (m, 3H), 2.32 (s, 3H), 2.27 – 2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.86, 159.75, 156.81, 143.41, 135.59, 131.01, 128.91, 127.82, 124.89, 115.86, 46.02, 32.03,

21.49, 19.63, 13.82. IR (KBr) *v*: 2921, 1667, 1544, 1438, 1167, 1087, 703 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{17}N_3O_3S_2$ $[M-H]^-$ 375.0728, found 375.0711.

2-Fluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10c). Yield 81%, light yellow solid, mp 162-163 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.73 – 7.65 (m, 1H), 7.52 – 7.42 (m, 1H), 7.16 – 7.05 (m, 2H), 3.95 (t, *J* = 7.4 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.56 (s, 3H), 2.27 – 2.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.81, 160.27 (d, *J* = 101.3 Hz), 158.24, 156.80, 134.95 (d, *J* = 8.4 Hz), 132.27, 130.50, 127.13 (d, *J* = 14.1 Hz), 123.86 (d, *J* = 3.7 Hz), 123.80, 116.90 (d, *J* = 21.5 Hz), 115.93, 46.06, 32.02, 19.56, 13.90. IR (KBr) *v*: 29218, 1666, 1544, 1439, 1173, 1106, 877 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{14}FN_3O_3S_2$ [M-H]- 379.0453, found 379.0461.

3-Fluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10d). Yield 84%, light yellow solid, mp 172-173 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.42 (ddd, *J* = 11.5, 8.2, 4.8 Hz, 2H), 7.30 (td, *J* = 8.0, 5.3 Hz, 1H), 7.14 (td, *J* = 8.3, 2.5 Hz, 1H), 3.94 (t, *J* = 7.4 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.61 (s, 3H), 2.27 – 2.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.08 (d, *J* = 209.8 Hz), 160.63, 159.88, 156.83, 140.49 (d, *J* = 6.8 Hz), 131.81, 130.03 (d, *J* = 7.6 Hz), 124.25, 123.70 (d, *J* = 3.5 Hz), 119.80 (d, *J* = 21.2 Hz), 115.66, 115.26 (d, *J* = 20.9 Hz), 46.01, 32.02, 19.57, 13.86. IR (KBr) *v*: 2921, 1666, 1543, 1463, 1166, 1085, 739 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{14}FN_3O_3S_2$ $[M-H]^-$ 379.0450, found 379.0461.

4-Fluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10e). Yield 85%, light yellow solid, mp 179-180 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H), 7.62 (s, 1H), 7.05 – 6.93 (m, 2H), 3.92 (t, *J* = 7.4 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.62 (s, 3H), 2.27 – 2.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ165.19 (d, *J* = 254.6 Hz), 161.10, 159.87, 156.80, 134.45 (d, *J* = 2.9 Hz), 131.92, 130.70 (d, *J* = 9.4 Hz), 124.48, 115.63 (d, *J* = 10.8 Hz), 115.35, 46.01, 32.02, 19.55, 13.85. IR (KBr) *v*: 29210, 1660, 1547, 1464, 1170, 1048, 708 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{14}FN_3O_3S_2$ $[M-H]^-$ 379.0472, found 379.0461.

4-Bromo-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10f). Yield 89%, white solid, mp 174-175 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 3.92 (t, *J* = 7.2 Hz, 2H), 3.10 (t, *J* = 7.9 Hz, 2H), 2.62 (s, 3H), 2.31 – 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.07, 159.94, 156.70, 137.29, 132.26, 131.49, 129.55, 127.69, 124.28, 115.75, 46.08, 32.06, 19.63, 13.82. IR (KBr) *v*: 2936, 1669, 1542, 1451, 1176, 1087, 742 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{14}BrN_3O_3S_2$ $[M-H]^-$ 438.9654, found 438.9660.

N-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-4-nitrobenzenesulfonamide (10g). Yield 74%, light yellow solid, mp 225-226 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.10 (m, 2H), 7.89 – 7.81 (m, 2H), 7.70 (s, 1H), 3.87 (t, *J* = 7.4 Hz, 2H), 3.08 (t, *J* = 8.0 Hz, 2H), 2.64 (s, 3H), 2.28-2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.37, 160.11, 156.73, 150.11, 144.12, 132.76, 129.23, 123.53, 123.45, 115.33, 46.06, 32.03, 19.42, 13.89. IR

(KBr) *v*: 2922, 1666, 1545, 1338, 1164, 1091, 684 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{14}N_4O_5S_2$ $[M-H]^-$ 406.0412, found 406.0406.

4-Methoxy-*N*-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidin-3-yl)benzenesulfonamide (10h). Yield 82%, light yellow solid, mp 248-249 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.63 – 7.56 (m, 2H), 6.81 – 6.72 (m, 2H), 3.93 (t, *J* = 7.4 Hz, 2H), 3.79 (s, 3H), 3.06 (d, *J* = 8.0 Hz, 2H), 2.60 (s, 3H), 2.27 – 2.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.96, 160.73, 159.68, 156.85, 131.24, 130.28, 130.05, 125.08, 115.95, 113.46, 55.55, 46.05, 32.01, 19.65, 13.76. IR (KBr) *v*: 2929, 1665, 1547, 1421, 1175, 1089, 757 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{17}N_3O_4S_2$ $[M-H]^-$ 391.0671, found 391.0660.

***N*-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*d*]pyrimidin-3-yl)-2-(trifluoromethyl)benzenesulfonamide (10i).** Yield 83%, light yellow solid, mp 203-204 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.54 (m, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 3.86 (t, *J* = 7.4 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.53 (s, 3H), 2.23 – 2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.62, 159.86, 156.30, 138.03, 133.29, 132.45, 131.53, 131.15, 128.83 (d, *J* = 35.4 Hz), 128.06 (q, *J* = 6.3 Hz), 124.01 (q, *J* = 3.5 Hz), 121.40, 115.94, 46.01, 32.01, 19.59, 13.89. IR (KBr) *v*: 2932, 1659, 1547, 1431, 1161, 1083, 789 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_3O_3S_2$ $[M-H]^-$ 429.0416, found 429.0429.

***N*-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-3-(trifluoromethyl)benzenesulfonamide (10j).** Yield 79%, light yellow solid, mp 191-192 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.82 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.61 (s, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 3.85(t, *J* = 7.4 Hz, 2H), 3.06 (t, *J* = 8.0 Hz, 2H), 2.64 (s, 3H), 2.24 – 2.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.22, 159.99, 156.63, 139.52, 132.77, 131.28, 130.77 (d, *J* = 33.5 Hz), 129.20, 129.10 (q, *J* = 3.7 Hz), 125.01 (q, *J* = 4.0 Hz), 124.51, 123.98, 115.54, 45.88, 31.98, 19.60, 13.74. IR (KBr) *v*: 2933, 1678, 1541, 1436, 1159, 1067, 743 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_3O_3S_2$ $[M-H]^-$ 429.0435, found 429.0429.

***N*-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-4-(trifluoromethyl)benzenesulfonamide (10k).** Yield 80%, white solid, mp 216-217 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.51 (s, 1H), 3.82 (t, *J* = 7.4 Hz, 2H), 3.06 (t, *J* = 8.0 Hz, 2H), 2.64 (s, 3H), 2.23 – 2.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.13, 160.02, 156.53, 141.71, 134.23 (q, *J* = 32.8 Hz), 132.92, 128.57, 125.27 (q, *J* = 3.6 Hz), 123.94, 122.92 (d, *J* = 33 Hz) 115.64, 45.95, 32.01, 19.52, 13.81. IR (KBr) *v*: 2923, 1662, 1547, 1407, 1165, 1061, 713 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_3O_3S_2$ $[M-H]^-$ 429.0422, found 429.0429.

***N*-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-2-(trifluoromethoxy)benzenesulfonamide (10l).** Yield 81%, light yellow solid, mp 158-159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.76 (s, 1H), 7.53 (td, *J* = 8.2, 1.7 Hz, 1H), 7.34 – 7.22 (m, 2H), 3.93(t, *J* = 7.4 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.51 (s, 3H), 2.26 – 2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.95, 159.76, 156.84, 146.64 (d, *J* = 1.8 Hz), 134.28, 131.82, 131.04, 126.13, 123.91, 121.35, 120.05, 118.76, 115.98, 46.02, 32.07, 19.59, 13.77. IR (KBr) *v*:

2933, 1663, 1545, 1240, 1156, 1047, 717 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_3O_4S_2$ $[M-H]^-$ 445.0384, found 445.0378.

N-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-3-(trifluoromethoxy)benzenesulfonamide (10m). Yield 83%, light yellow solid, mp 153-154 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.9 Hz, 1H), 7.61 (s, 1H), 7.42 (dd, *J* = 9.8, 6.2 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 1H), 3.86 (t, *J* = 7.4 Hz, 2H), 3.06 (t, *J* = 8.0 Hz, 2H), 2.63 (s, 3H), 2.25 – 2.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.19, 159.86, 156.65, 148.53 (d, *J* = 3.7 Hz), 140.38, 132.45, 129.99, 126.55, 125.32, 123.98, 120.64, 118.77, 115.48, 45.83, 31.94, 19.57, 13.76. IR (KBr) *v*: 2921, 1667, 1544, 1438, 1167, 1087, 703 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_3O_4S_2$ $[M-H]^-$ 445.0380, found 4445.0378.

N-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-4-(trifluoromethoxy)benzenesulfonamide (10n). Yield 88%, light yellow solid, mp 181-182 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H), 7.53 (s, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 3.87 (t, *J* = 7.4 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.63 (s, 3H), 2.25 – 2.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.07, 159.89, 156.64, 152.14 (q, *J* = 1.4 Hz), 136.67, 132.62, 130.16, 120.33, 120.16 (q, *J* = 258 Hz), 115.66, 110.03, 45.94, 31.97, 19.46, 13.78. IR (KBr) *v*: 2928, 1652, 1544, 1,342, 1155, 1090, 784 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_3O_4S_2$ $[M-H]^-$ 445.0375, found 445.0378.

3,5-Difluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10o). Yield 81%, light yellow solid, mp 201-202 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.23 (dd, *J* = 6.4, 2.2 Hz, 2H), 6.89 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.97 (t, *J* = 7.4 Hz, 2H), 3.11 (t, *J* = 8.0 Hz, 2H), 2.61 (s, 3H), 2.30 – 2.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.19 (dd, *J* = 254.0, 11.4 Hz), 161.31, 160.06, 156.91, 141.84 (t, *J* = 8.5 Hz), 132.31, 123.74, 115.54, 111.46 (q, *J* = 27.9 Hz), 108.17 (t, *J* = 25.0 Hz), 46.10, 32.06, 19.59, 13.87. IR (KBr) *v*: 2926, 1667, 1545, 1435, 1166, 1089, 782 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{13}F_2N_3O_3S_2$ $[M-H]^-$ 397.0361, found 397.0366.

3,4-Difluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10p). Yield 85%, light yellow solid, mp 219-220 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.59 – 7.51 (m, 1H), 7.48 – 7.41 (m, 1H), 7.11 (dd, *J* = 16.9, 8.8 Hz, 1H), 3.96 (t, *J* = 7.2 Hz, 2H), 3.11 (t, *J* = 7.9 Hz, 2H), 2.61 (s, 3H), 2.30 – 2.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.24, 160.04, 156.87, 153.14 (dd, *J* = 256.2, 11.7 Hz), 149.53 (dd, *J* = 253.0, 14.1 Hz), 135.24 (t, J = 3.9 Hz), 132.26, 125.15 (dd, J = 7.6, 4.0 Hz), 124.01, 117.94 (d, J = 19.3 Hz), 117.34 (d, J = 18.2 Hz), 115.58, 46.17, 32.13, 19.59, 13.82. IR (KBr) *v*: 2921, 1655, 1547, 1437, 1164, 1087, 688 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{13}F_2N_3O_3S_2$ $[M-H]^-$ 397.0361, found 397.0366.

2,6-Difluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10q). Yield 89%, light yellow solid, mp 179-180 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.41 (t, *J* = 6.9 Hz, 1H), 6.89 (t, *J* = 8.7 Hz, 2H), 3.95 (t, *J* = 7.0 Hz, 2H), 3.11 (t, *J* = 7.4 Hz, 2H), 2.59 (s, 3H), 2.28 – 2.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.99 (dd, *J* =

260.9, 3.6 Hz), 160.97, 159.80, 156.81, 134.43 (t, *J* = 9.1 Hz), 132.95, 123.15, 117.06 (d, *J* = 15.7 Hz), 115.81, 159.99 (dd, *J* = 260.9, 3.6 Hz), 46.18, 32.14, 19.61, 13.94. IR (KBr) *v*: 2926, 1668, 1651, 1544, 1463, 1179, 1000, 771 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{13}F_2N_3O_3S_2$ $[M-H]^-$ 397.0359, found 397.0366.

2,5-Difluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10r). Yield 82%, light yellow solid, mp 162-163 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.43 – 7.35 (m, 1H), 7.16 (ddd, *J* = 12.2, 7.0, 3.3 Hz, 1H), 7.08 (td, *J* = 8.9, 4.0 Hz, 1H), 3.97 (t, *J* = 7.4 Hz, 2H), 3.12 (t, *J* = 8.0 Hz, 2H), 2.56 (s, 3H), 2.29 – 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.14, 159.90, 157.71 (dd, *J* = 171.3, 2.4 Hz), 156.95, 155.22 (dd, *J* = 178.3, 2.6 Hz), 132.92, 128.38 (dd, *J* = 16.6, 6.8 Hz), 123.34, 121.45 (dd, *J* = 23.8, 8.5 Hz), 118.20 (dd, *J* = 24.6, 7.7 Hz), 117.08 (d, *J* = 27.0 Hz), 115.84, 46.11, 32.06, 19.55, 13.91. IR (KBr) *v*: 2927, 1662, 1545, 1488, 1170, 833 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{13}F_2N_3O_3S_2$ $[M-H]^-$ 397.0364, found 397.0366.

2,4-Difluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10s). Yield 77%, light yellow solid, mp 176-177 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.75 – 7.61 (m, 1H), 6.83 (t, *J* = 8.5 Hz, 2H), 3.96 (t, *J* = 7.4 Hz, 2H), 3.11 (t, *J* = 8.0 Hz, 2H), 2.57 (s, 3H), 2.29 – 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.80 (dd, *J* = 257.9, 12.1 Hz), 161.12, 160.46 (dd, *J* = 265.0, 16.8 Hz), 159.88, 156.83, 132.96, 132.27 (dd, *J* = 16.5, 6.87Hz), 123.56, 123.54 (dd, *J* = 14.2, 3.9 Hz), 115.82, 111.26 (dd, *J* = 21.8, 3.9 Hz), 105.30 (t, *J* = 25.6 Hz), 46.12, 32.03 – 31.83 (m), 19.62, 14.03. IR (KBr) *v*: 2919, 1658, 1598, 1426, 1174, 971, 740 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{13}F_2N_3O_3S_2$ $[M-H]^-$ 397.0369, found 397.0366.

3-Fluoro-4-methyl-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10t). Yield 79%, light yellow solid, mp 184-185 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.41 – 7.31 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 3.95 (t, *J* = 7.3 Hz, 2H), 3.10 (t, *J* = 7.9 Hz, 2H), 2.59 (s, 3H), 2.29 – 2.18 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.23 (d, *J* = 55.2 Hz), 159.79, 159.03, 156.90, 137.71 (d, *J* = 7.0 Hz), 131.38, 131.33 (d, *J* = 4.8 Hz), 130.48 (d, *J* = 17.3 Hz), 124.50, 123.43 (d, *J* = 3.9 Hz), 115.74, 114.80 (d, *J* = 25.7 Hz), 46.04, 32.04, 19.64, 14.75 (d, J = 3.7 Hz), 13.89. IR (KBr) *v*: 2922, 1663, 1544, 1402, 1154, 709 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{16}FN_3O_3S_2$ $[M-H]^-$ 393.0610, found 393.0617.

2-Methyl-4-fluoro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10u). Yield 85%, white solid, mp 193-194 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.65 (s, 1H), 6.88 (d, *J* = 9.5 Hz, 1H), 6.83 (t, *J* = 8.3 Hz, 1H), 3.97 (t, *J* = 7.3 Hz, 2H), 3.11 (t, *J* = 8.0 Hz, 2H), 2.58 (s, 3H), 2.49 (s, 3H), 2.30 – 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.76 (d, *J* = 254.2 Hz), 160.97, 159.87, 156.94, 142.17 (d, *J* = 9.1 Hz), 133.27, 132.84 (d, *J* = 9.5 Hz), 131.35, 124.55, 118.84 (d, *J* = 21.9 Hz), 115.98, 112.74 (d, *J* = 21.8 Hz), 46.07, 32.04, 21.15, 19.59, 13.81. IR (KBr) *v*: 2925, 1664, 1540, 1456, 1160, 935, 707 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{16}FN_3O_3S_2$ $[M-H]^-$ 393.0613, found 393.0617.

***4-Chloro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-3-nitrobenzenesulfonamide (10v)*.** Yield 72%, light yellow solid, mp 191-192 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.61 (s, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 3.68 (t, *J* = 6.1 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.65 (s, 3H), 1.97 – 1.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.84, 158.67, 156.73, 148.98, 139.88, 134.17, 131.93, 131.51, 129.13, 125.55, 124.09, 116.63, 41.70, 32.77, 18.81, 13.69. IR (KBr) *v*: 2924, 1662, 1540, 1343, 1170, 1046, 776 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{13}ClN_4O_5S_2$ $[M-H]^-$ 440.0023, found 440.0016.

***3,5-Dichloro-N-(2-methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)benzenesulfonamide (10w)*.** Yield 76%, light yellow solid, mp 202-203 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.55 (d, *J* = 1.8 Hz, 2H), 7.41 (t, *J* = 1.7 Hz, 1H), 3.97 (t, *J* = 7.4 Hz, 2H), 3.11 (t, *J* = 7.9 Hz, 2H), 2.61 (s, 3H), 2.32 – 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.30, 160.07, 156.81, 141.19, 135.16, 132.71, 132.43, 126.42, 123.70, 115.60, 46.09, 32.10, 19.71, 13.79. IR (KBr) *v*: 2930, 1658, 1548, 1342, 1172, 937, 780 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{13}Cl_2N_3O_3S_2$ $[M-H]^-$ 428.9780, found 428.9775.

***N-(2-Methyl-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]thieno[2,3-d]pyrimidin-3-yl)-[1,1'-biphenyl]-4-sulfonamide (10x)*.** Yield 82%, light yellow solid, mp 167-168 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.65 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 4H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.41 – 7.35 (m, 1H), 3.82 (t, *J* = 7.1 Hz, 2H), 2.99 (t, *J* = 7.7 Hz, 2H), 2.62 (s, 3H), 2.09-2.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.89, 159.70, 156.73, 145.36, 139.17, 136.86, 131.71, 129.07, 128.53, 128.50, 127.04, 126.69, 124.79, 115.93, 45.95, 31.96, 19.43, 13.84. IR (KBr) *v*: 2929, 1651, 1549, 1456, 1166, 1090, 765 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{19}N_3O_3S_2$ $[M-H]^-$ 437.0683, found 437.0688

***N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11a)*.** Yield 91%, light yellow solid, mp 173-174 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 4.06 (t, *J* = 4.8Hz, 2H), 2.93 (t, *J* = 4Hz, 2H), 2.62 (s, 3H), 1.82-1.71 (m, 4H), 1.61-150 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.86, 159.02, 157.59, 138.35, 132.55, 131.76, 128.19, 127.93, 125.02, 115.42, 41.83, 37.21, 29.30, 27.49, 24.93, 13.79. IR (KBr) *v*: 2926, 1654, 1576, 1410, 1165, 1090, 624 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{19}N_3O_3S_2$ $[M-H]^+$ 389.0861, found 389.0868.

***4-Methyl-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11b)*.** Yield 85%, white solid, mp 179-180 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.07 (t, *J* = 4.8 Hz, 2H), 2.94 (t, *J* = 4Hz, 2H), 2.61 (s, 3H), 2.30 (s, 3H), 1.83 – 1.71 (m, 4H), 1.60-1.52(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.82, 158.70, 157.52, 143.28, 135.51, 131.70, 128.79, 127.95, 125.23, 115.55, 41.81, 37.08, 29.34, 27.42, 24.96, 21.47, 13.78. IR (KBr) *v*: 2921, 1663, 1573, 1488, 1159, 1088, 671cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{21}N_3O_3S_2$ $[M-H]^-$ 403.1030, found 403.1024.

2-Fluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11c). Yield 83%, light yellow solid, mp 158-159 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.71 – 7.64 (m, 1H), 7.49 – 7.42 (m, 1H), 7.13 – 7.03 (m, 2H),4.09 (t, *J* = 4.8 Hz, 2H), 2.95 (t, *J* = 4.1 Hz, 2H), 2.57 (s, 3H), 1.82 – 1.72 (m, 4H), 1.63-1.54(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.88, 159.58 (d, *J* = 258.3 Hz), 159.07, 157.67, 134.86 (d, *J* = 8.3 Hz), 132.51, 130.64, 126.95 (d, *J* = 13.9 Hz), 124.12, 123.76 (d, *J* = 3.9 Hz), 116.81 (d, *J* = 21.6 Hz), 115.39, 41.88, 37.25, 29.36, 27.52, 24.94, 13.85. IR (KBr) *v*: 2923, 1656, 1578, 1478, 1157, 1073, 717 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}FN_3O_3S_2$ $[M-H]^-$ 407.0767, found 407.0774.

3-Fluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11d). Yield 86%, light yellow solid, mp 175-176 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.45 – 7.41 (m, 1H), 7.41 – 7.37 (m, 1H), 7.31 – 7.24 (m, 1H), 7.17 – 7.08 (m, 1H), 4.10 (t, *J* = 4.8 Hz, 2H), 2.95 (t, *J* = 4Hz, 2H), 2.62 (s, 3H), 1.82-1.71 (d, *J* = 2.5 Hz, 4H), 1.64-1.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.83 (d, *J* = 250.6 Hz), 160.06, 159.03, 157.62, 140.37 (d, *J* = 6.9 Hz), 132.18, 129.89 (d, *J* = 7.6 Hz), 124.54, 123.74 (d, *J* = 3.2 Hz), 119.72 (d, *J* = 44 Hz), 115.32 (d, *J* = 44 Hz), 115.27, 41.93, 37.18, 29.31, 27.44, 24.90, 13.79. IR (KBr) *v*: 2923, 1653, 1507, 1477, 1164, 698 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}FN_3O_3S_2$ $[M-H]^-$ 407.0770, found 407.0774.

4-Fluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11e). Yield 87%, light yellow solid, mp 169-170 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.65 – 7.60 (m, 2H), 7.02 – 6.91 (m, 2H), 4.09 (t, *J* = 4.8 Hz, 2H), 2.95 (t, *J* = 4 Hz, 2H), 2.62 (s, 3H), 1.84 – 1.72 (m, 4H), 1.62-1.53(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.16 (d, *J* = 254.7 Hz), 160.07, 159.21, 157.56, 134.34 (d, *J* = 2.9 Hz), 132.32, 130.74 (d, *J* = 9.4 Hz), 124.75, 115.34, 115.31 (d, *J* = 9.4 Hz), 41.92, 37.22, 29.26, 27.46, 24.92, 13.74. IR (KBr) *v*: 2926, 1659, 1577, 1490, 1164, 1087, 836 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}FN_3O_3S_2$ $[M-H]^-$ 407.0765, found 407.0774.

4-Bromo-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11f). Yield 90%, light yellow solid, mp 168-169 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 4.07 (t, *J* = 4.8 Hz, 2H), 2.95 (t, *J* = 4 Hz, 2H), 2.63 (s, 3H), 1.85-1.73 (m 4H), 1.65-1.56(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.90, 159.82, 158.95, 157.58, 131.74, 130.08, 130.05, 125.35, 115.60, 113.28, 55.43, 41.80, 37.18, 29.28, 27.42, 24.96, 13.75. IR (KBr) *v*: 2921 1660, 1581, 1337, 1161, 1064, 739cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}BrN_3O_3S_2$ $[M-H]^-$ 466.9965, found 466.9973.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-4-nitrobenzenesulfonamide (11g). Yield 73%, white solid, mp 224-225 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 2H), 7.87 – 7.80 (m, 2H), 7.69 (s, 1H), 4.01 (t, *J* = 4.8 Hz, 2H), 2.94 (t, *J* = 4 Hz, 2H), 2.65 (s, 3H), 1.79 – 1.70 (m, 4H), 1.50(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.29, 159.17, 157.47, 150.10, 144.02, 133.15, 129.31, 123.65, 123.31, 114.96, 41.88, 37.07, 29.12,

27.32, 24.82, 13.78. IR (KBr) *v*: 2921, 1654, 1577, 1416, 1341, 1169, 1088, 781 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{18}N_4O_5S_2$ $[M-H]^-$ 434.0712, found 434.0719.

4-Methoxy-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11h). Yield 77%, light yellow solid, mp 150-151 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.59 – 7.51 (m, 2H), 6.79 – 6.70 (m, 2H), 4.09 (t, *J* = 4.8 Hz, 2H), 3.77 (s, 3H), 2.94 (t, *J* = 4Hz, 2H), 2.61 (s, 3H), 1.83-1.72 (m, 4H), 1.61-1.52(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.87, 159.78, 158.92, 157.55, 131.68, 130.08, 130.04, 125.31, 115.57, 113.24, 55.40, 41.76, 37.14, 29.24, 27.39, 24.92, 13.71. IR (KBr) *v*: 2925, 1661, 1580, 1415, 1335, 1167, 1079, 739 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{21}N_3O_4S_2$ $[M-H]^-$ 419.0967, found 419.0973.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-2-(trifluoromethyl)benzenesulfonamide (11i). Yield 73%, light yellow solid, mp 136-137 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.62 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 3.67 (t, *J* = 6.1 Hz, 2H), 2.88 (t, *J* = 6.8 Hz, 2H), 2.53 (s, 3H), 1.96-1.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.07, 158.85, 156.79, 139.09, 133.28, 132.96, 131.85, 131.58, 129.51 (d, *J* = 33.6 Hz), 128.39 (q, *J* = 6.3 Hz), 125.73 (q, *J* = 3.7 Hz), 124.34, 115.92, 41.76, 37.27, 29.58, 27.61, 24.83, 13.69. IR (KBr) *v*: 2928, 1653, 1575, 1413, 1346, 1169, 1081, 762 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}F_3N_3O_3S_2$ $[M-H]^-$ 457.0749, found 457.0742.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-3-(trifluoromethyl)benzenesulfonamide (11j). Yield 84%, light yellow solid, mp 170-171 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.9 Hz, 1H), 7.80 (s, 1H), 7.68 (d, *J* = 6.6 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 4.02 (t, *J* = 4.8 Hz, 2H), 2.93(t, *J* = 4Hz, 2H), 2.64 (s, 3H), 1.81-1.70 (m, 4H), 1.60-1.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.20, 159.29, 157.44, 139.39, 132.95, 131.24, 130.79 (d, *J* = 33.3 Hz), 129.05, 129.01 (d, *J* = 6.4, Hz), 125.08 (q, *J* = 3.9 Hz), 124.23, 115.11, 41.84, 37.21, 29.35, 27.43, 24.83, 13.73. IR (KBr) *v*: 2927, 1655, 1575, 1327, 1125, 724 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}F_3N_3O_3S_2$ $[M-H]^-$ 457.0737, found 457.0742.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-4-(trifluoromethyl)benzenesulfonamide (11k). Yield 82%, light yellow solid, mp 167-168 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 3.2 Hz, 2H),, 7.68 (s, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 4.00 (t, *J* = 4.8Hz, 2H), 2.93 (t, *J* = 4Hz, 2H), 2.64 (s, 3H), 1.80 – 1.69 (m, 4H), 1.56-1.43(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.20, 159.33, 157.46, 141.71, 134.24 (q, *J* = 32.9 Hz), 132.92, 125.20 (q, *J* = 3.7 Hz), 124.58, 124.21, 121.85, 115.18, 41.85, 37.18, 29.23, 27.34, 24.83, 13.81. IR (KBr) *v*: 2924, 1671, 1577, 1319, 1160, 780 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}F_3N_3O_3S_2$ $[M-H]^-$ 457.0734, found 457.0742.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-2-(trifluoromethoxy)benzenesulfonamide (11l). Yield 79%, light yellow solid, mp 161-162 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.85 (s, 1H), 7.57 (td, *J* = 8.1, 1.7 Hz, 1H), 7.35 – 7.27 (m, 2H), 3.81 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 6.5 Hz, 1H), 2.64 (s, 3H), 1.92 – 1.85 (m,

6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.09, 159.21, 156.02, 147.39, 134.91, 132.15, 132.55, 131.72, 126.85, 124.22, 120.57 (d, *J* = 260.0 Hz), 119.67 (q, *J* = 5.8Hz), 115.21, 41.83, 37.24, 29.48, 27.25, 24.27, 13.70. IR (KBr) *v*: 2925, 1655, 1581, 1215, 1151, 1073, 738 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}F_3N_3O_4S_2$ $[M-H]^-$ 473.0695, found 473.0691.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-3-(trifluoromethoxy)benzenesulfonamide (11m). Yield 81%, white solid, mp 142-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.42 (s, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 17.8 Hz, 1H), 4.05 – 4.00 (m, 2H), 2.95 – 2.89 (m, 2H), 2.61 (s, 3H), 1.75 – 1.53 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.03, 159.26, 157.50, 148.55 (q, *J* =2.8 Hz), 140.25, 132.55, 129.81, 126.46, 125.11, 124.27, 120.64, 120.09 (q, *J* = 258.8 Hz), 115.06, 41.78, 37.17, 29.31, 27.39, 24.78, 13.73. IR (KBr) *v*: 2922, 1663, 1580, 1488, 1254, 1161, 725 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}F_3N_3O_4S_2$ $[M-H]^-$ 473.0688, found 473.0691.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-4-(trifluoromethoxy)benzenesulfonamide (11n). Yield 85%, light yellow solid, mp 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 3.2 Hz, 2H),, 7.68 (s, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 4.00 (t, *J* = 4.8Hz, 2H), 2.93 (t, *J* = 4Hz, 2H), 2.64 (s, 3H), 1.80 – 1.69 (m, 4H), 1.56-1.43(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.20, 159.33, 157.46, 152.12 (q, *J* = 2.0 Hz), 136.57, 132.59, 130.14, 124.48, 119.4, 120.10 (q, *J* = 259.2 Hz), 115.18, 41.85, 37.18, 29.23, 27.34, 24.83, 13.81. IR (KBr) *v*: 2923, 1655, 1578, 1488, 1250, 1151, 629 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}F_3N_3O_4S_2$ $[M-H]^-$ 473.0684, found 473.0691.

3,5-Difluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11o). Yield 80%, light yellow solid, mp 205-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.21 (dt, *J* = 6.0, 3.7 Hz, 2H), 6.88 (tt, *J* = 8.4, 2.3 Hz, 1H), 4.13 (t, *J* = 4.8Hz, 2H), 2.97 (t, *J* = 4Hz, 2H), 2.61 (s, 3H), 1.84-1.73 (m, 4H), 1.67-1.59(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.31 (dd, *J* = 254.0, 11.4 Hz), 160.11, 158.46., 156.03, 138.84 (t, *J* = 8.5 Hz), 132.79, 125.14, 115.54, 113.45 (q, *J* = 27.9 Hz), 109.38 (t, *J* = 25.0 Hz), 41.84, 37.31, 29.37, 27.51, 24.89, 13.71. IR (KBr) *v*: 2924, 1655, 1578, 1487, 1251, 1160, 631 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}F_2N_3O_3S_2$ $[M-H]^-$ 425.0675, found 425.0679.

3,4-Difluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11p). Yield 83%, light yellow solid, mp 177-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.51 (ddd, *J* = 9.5, 7.3, 2.2 Hz, 1H), 7.42 – 7.30 (m, 1H), 7.15 – 6.95 (m, 1H), 4.12 (t, *J* = 4.8Hz, 2H), 2.97 (t, *J* = 4Hz, 2H), 2.61 (s, 3H), 1.84-1.73 (m, 4H), 1.65-1.58(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.20, 159.41, 157.64, 153.07 (dd, *J* = 256.4, 12.1 Hz), 149.43 (dd, *J* = 255.3, 12.3 Hz), 135.12 (d, *J* = 24.0 Hz), 132.68, 125.21 (d, *J* = 21.3 Hz), 124.27, 117.95 (d, *J* = 20.0 Hz), 117.11 (d, *J* = 17.8 Hz), 115.20, 41.94, 37.24, 29.27, 27.41, 24.91, 13.75. IR (KBr) *v*: 2924, 1668, 1579, 1483, 1161, 1090, 623 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}F_2N_3O_3S_2$ $[M-H]^-$ 425.0671, found 425.0679.

***2,6-Difluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11q)*.** Yield 89%, light yellow solid, mp 204-205 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.39 (tt, *J* = 8.4, 5.8 Hz, 1H), 6.87 (t, *J* = 8.6 Hz, 2H), 4.10 (t, *J* = 4.8Hz, 2H), 2.96 (t, *J* = 4Hz, 2H), 2.59 (s, 3H), 1.83-1.72(m, 4H), 1.62-1.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.05 (dd, *J* = 261.1, 3.7 Hz), 159.92, 159.25, 157.69, 134.36 (t, *J* = 10.9 Hz), 133.21, 123.33, 117.01 (t, J = 15.2 Hz), 115.28, 112.58 (dd, *J* = 23.5, 3.7 Hz), 41.89, 37.26, 29.36, 27.58, 24.93, 13.80. IR (KBr) *v*: 2923, 1656, 1575, 1470, 1166, 1000, 790 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}F_2N_3O_3S_2$ $[M-H]^-$ 425.0682, found 425.0679.

***2,5-Difluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11r)*.** Yield 82%, white solid, mp 148-149 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.40 – 7.31 (m, 1H), 7.15 (ddt, *J* = 9.2, 7.0, 3.4 Hz, 1H), 7.04 (td, *J* = 8.9, 4.0 Hz, 1H), 4.13(t, *J* = 4.8Hz, 2H), 2.97 (t, *J* = 4Hz, 2H), 2.57 (s, 3H), 1.84-1.73 (m, 4H), 1.65-1.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.08, 159.26, 157.67, 157.29 (dd, *J* = 247.2, 2.7 Hz), 155.60 (dd, *J* = 254.5, 2.8 Hz), 133.14, 128.16 (dd, *J* = 16.9, 6.9 Hz), 123.58, 121.36 (dd, *J* = 23.9, 8.5 Hz), 118.09 (dd, *J* = 24.6, 7.7 Hz), 117.17 (d, *J* = 27 Hz), 115.38, 41.95, 37.25, 29.34, 27.51, 24.90, 13.90. IR (KBr) *v*: 2927, 1662, 1578, 1475, 1163, 1007, 725 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}F_2N_3O_3S_2$ $[M-H]^-$ 425.0686, found 425.0679.

***2,4-Difluoro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11s)*.** Yield 79%, light yellow solid, mp 169-170 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.67 – 7.61 (m, 1H), 6.80 (ddd, *J* = 9.5, 4.4, 2.6 Hz, 2H), 4.11(t, *J* = 4.8Hz, 2H), 2.96 (t, *J* = 4Hz, 2H), 2.58 (s, 3H), 1.83 – 1.75 (m, 4H), 1.65-1.58(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.80 (dd, *J* = 257.7, 12.0 Hz), 160.52 (dd, *J* = 262.9, 14.6 Hz), 160.02, 159.19, 157.63, 133.35, 132.46 (dd, *J* = 6.8, 5.4 Hz), 123.81, 123.33 (dd, *J* = 10.3, 7.9 Hz), 115.36, 111.13 (dd, *J* = 18.6, 7.2 Hz), 105.17 (d, J = 25.2Hz), 41.90, 37.24, 29.32, 27.50, 24.93, 13.81. IR (KBr) *v*: 2929, 1670, 1564, 1482, 1168, 1071, 738 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}F_2N_3O_3S_2$ $[M-H]^-$ 425.0683, found 425.0679.

***3-Fluoro-4-methyl-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11t)*.** Yield 77%, light yellow solid, mp 200-201 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.35 – 7.27 (m, 2H), 7.11 (t, *J* = 7.7 Hz, 1H), 4.10(t, *J* = 4.8Hz, 2H), 2.96 (t, J = 4Hz, 2H), 2.61 (s, 3H), 2.23 (d, *J* = 1.8 Hz, 3H), 1.84-1.75 (m, 4H), 1.63-1.55(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.42, 159.96, 158.99 (d, *J* = 8.7 Hz), 157.64, 137.59 (d, *J* = 7.0 Hz), 131.91, 131.14 (d, *J* = 4.9 Hz), 130.37 (d, *J* = 17.1 Hz), 124.77, 123.50 (d, *J* = 3.7 Hz), 115.37, 114.86 (d, *J* = 24.6Hz), 41.87, 37.15, 29.26, 27.40, 24.95, 14.70 (d, *J* = 3.6 Hz), 13.78. IR (KBr) *v*: 2923, 1673, 1576, 1409, 1157, 673 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}FN_3O_3S_2$ $[M-H]^-$ 421.0921, found 421.0930.

***4-Fluoro-2-methyl-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11u)*.** Yield 79%, light yellow solid, mp 125-126 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H)7.73 – 7.66 (m, 1H), 6.85 (dd, *J* = 9.5, 2.5 Hz, 1H), 6.79 (td, *J* = 8.4,

2.6 Hz, 1H), 4.11(t, *J* = 4.8Hz, 2H), 2.96 (t, *J* = 4Hz, 2H), 2.55 (s, 3H), 2.52 (s, 3H), 1.84-1.74 (m, 4H), 1.67-1.58(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.02, 159.11, 157.72, 142.25 (d, *J* = 9.2 Hz), 133.01 (dd, *J* = 20.4, 6.2 Hz), 131.73, 124.81, 118.81, 118.60, 115.54, 112.70, 112.49, 41.90, 37.25, 29.32, 27.46, 24.93, 21.16, 13.77. IR (KBr) *v*: 2928, 1667, 1579, 1410, 1163, 950, 686 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}FN_3O_3S_2$ $[M-H]^-$ 421.0925, found 421.0930.

4-Chloro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-3-nitrobenzenesulfonamide (11v). Yield 75%, light yellow solid, mp 211-212 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.1 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.62 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H),4.07(t, *J* = 4.8Hz, 2H), 2.97 (t, *J* = 4Hz, 2H), 2.63 (s, 3H), 1.85-1.74(m, 4H), 1.63-1.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.53, 159.62, 157.50, 147.41, 138.44, 134.08, 131.93, 131.74, 130.96, 124.94, 123.46, 114.98, 42.06, 37.26, 29.35, 27.38, 24.83, 13.71. IR (KBr) *v*: 2927, 1664, 1577, 1423, 1160, 760 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}ClN_4O_5S_2$ $[M-H]^-$ 468.0334, found 468.0329.

3,5-Dichloro-N-(2-methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)benzenesulfonamide (11w). Yield 81%, light yellow solid, mp 184-185 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.51 (d, *J* = 1.8 Hz, 2H), 7.39 (t, *J* = 1.8 Hz, 1H), 4.13(t, *J* = 4.8Hz, 2H), 2.98 (t, *J* = 4Hz, 2H), 2.62 (s, 3H), 1.87-1.79 (m, 4H), 1.69-1.61 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 160.24, 159.36, 157.61, 141.05, 135.11, 132.99, 132.36, 126.39, 123.98, 115.15, 42.02, 37.28, 29.38, 27.49, 24.89, 13.76. IR (KBr) *v*: 2922, 1664, 1584, 1342, 1171, 799 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{17}Cl_2N_3O_3S_2$ $[M-H]^-$ 457.0082, found 457.0088.

N-(2-Methyl-4-oxo-4,6,7,8,9,10-hexahydrothieno[2',3':4,5]pyrimido[1,2-a]azepin-3-yl)-[1,1'-biphenyl]-4-sulfonamide (11x). Yield 85%, white solid, mp 170-171 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 4H), 7.41 (m, 3H), 3.99 (t, *J* = 4.8Hz, 2H), 2.87 (t, *J* = 4Hz, 2H), 2.65 (s, 3H), 1.68 – 1.54 (m, 4H), 1.45-1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.92, 158.91, 157.52, 145.28, 138.97, 136.79, 132.03, 129.02, 128.52, 128.43, 127.00, 126.52, 125.06, 115.53, 41.77, 37.05, 29.10, 27.31, 24.83, 13.77. IR (KBr) *v*: 2931, 1670, 1575, 1424, 1180, 781 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{23}N_3O_3S_2$. $[M-H]^-$ 465.1174, found 465.1181

Biology

Materials and methods. Murine B16 melanoma cell lines (B16F10) were obtained from CAS (Chinese Academy of Sciences, China). The B16F10 cells were grown in DMEM medium (GIBICO, USA) supplemented with 10% heat-inactivated fetal bovine serum (GIBICO, USA), 100 U/mL penicillin and 100 mg/mL streptomycin (GIBCO, USA) in a humidified atmosphere with 5% CO_2 at 37 °C.

Melanin contents assay

Exponentially growing cells were seeded into 6-well plates at a concentration of 5 x 10^5 cells per well. After 24 h incubation at 37 °C, the culture medium was removed and replaced with fresh medium containing the candidate compounds in different concentrations. The cells were incubated for another 48 h, washed with ice cold PBS, followed by lysis with RIPA buffer for 40 min on ice, and the lysates were centrifuged at 10,000 g for 20 min. Supernatants containing protein were subject to the protein assay and the pellets with intracellular melanin were solubilized in 200 µl of 1 M NaOH for 2 h at 60 °C. Melanin amount was determined spectrophotometrically at 405 nm by a multi-plate reader. The melanin amount was calculated by normalizing the total melanin values with protein content (abs melanin/lg protein).

Conclusion

In summary, herein we have reported the synthesis and evaluation of two novel series of 3-sulfonylamide containing pyrrolo- and azepino[1,2-*a*]thieno[2,3-*d*]pyrimidinone derivatives on melanin synthesis in murine B16 cells. Likewise, cycloalkane side-ring influences and various versions of *ipso*-nitration reactions toward a produce target sulfonamide derivatives were also developed. In general, some of synthesized tricyclic thieno[2,3-*d*]pyrimidinones showed promising potency. These results suggest that by the increasing of the thieno[2,3-*d*]pyrimidinone side-ring, the activity of the prepared samples were also increased, when substituents were at *m*- or *o*- positions (for example: from pyrrolo-, pyrido- and azepino- side-rings, compounds activity increased by following regularity: *p*-CF_3<*m*-CF_3, *o*-CF_3. Thus, the obtained results suggest that side-ring optimization influenced on melanin synthesis in murine B16 cells and further biological evaluation of other novel tricyclic thieno[2,3-*d*]pyrimidinone derivatives is ongoing and will be reported in due course.

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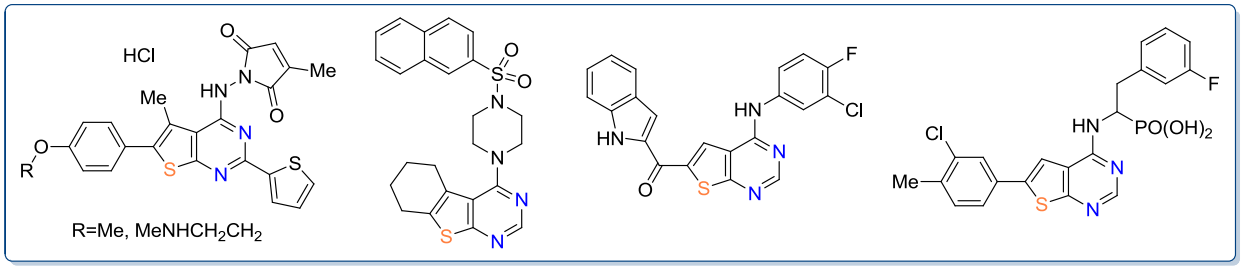
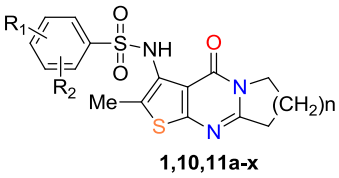


Figure 1. Biologically relevant thieno[2,3-*d*]pyrimidine scaffolds.

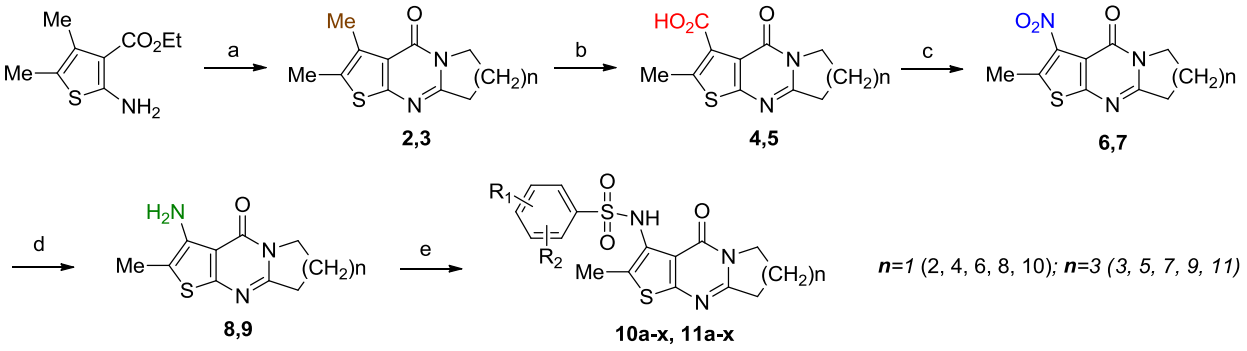


1,10,11a-x

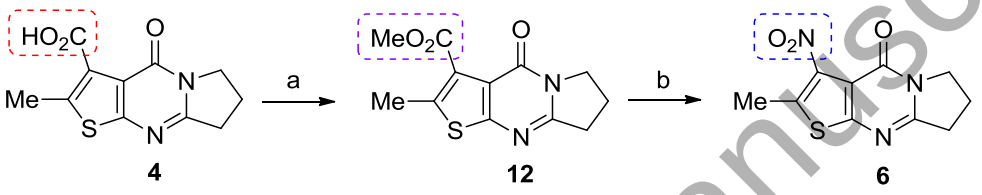
1,n=2, **10**, n=1, **11**, n=3

1,10,11a R_1=H, R_2=H
1,10,11b R_1=H, R_2=4-CH_3
1,10,11c R_1=H, R_2=2-F
1,10,11d R_1=H, R_2=3-F
1,10,11e R_1=H, R_2=4-F
1,10,11f R_1=H, R_2=4-Br
1,10,11g R_1=H, R_2=4-NO_2
1,10,11h R_1=H, R_2=4-OCH_3
1,10,11i R_1=H, R_2=2-CF_3
1,10,11j R_1=H, R_2=3-CF_3
1,10,11k R_1=H, R_2=4-CF_3
1,10,11l R_1=H, R_2=2-OCF_3
1,10,11m R_1=H, R_2=3-OCF_3
1,10,11n R_1=H, R_2=4-OCF_3
1,10,11o R_1=3-F, R_2=5-F
1,10,11p R_1=3-F, R_2=4-F
1,10,11q R_1=2-F, R_2=6-F
1,10,11r R_1=2-F, R_2=5-F
1,10,11s R_1=2-F, R_2=4-F
1,10,11t R_1=3-F, R_2=4-CH_3
1,10,11u R_1=4-F, R_2=2-CH_3
1,10,11v R_1=3-NO_2, R_2=4-Cl
1,10,11w R_1=3-Cl, R_2=5-Cl
1,10,11x R_1=H, R_2=4-Ph

Chart 1

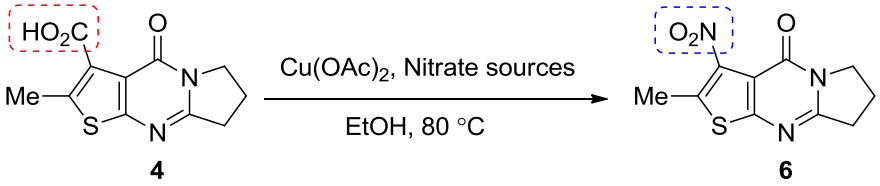


Scheme 1. Reagents and conditions: (a) appropriate lactams, $POCl_3$; (b) HNO_3/H_2SO_4; (c) $Cu(OAc)_2$ and $AgNO_3$, EtOH; (d) $SnCl_2 \cdot 2H_2O$, HCl, EtOH; (e) appropriate benzensulfonyl chlorides, dichloromethane, pyridine.



Scheme 2. Pathway 1. Reagents and conditions: (a) H_2SO_4, MeOH, reflux; (b) HNO_3/H_2SO_4, -10 – 0 °C.

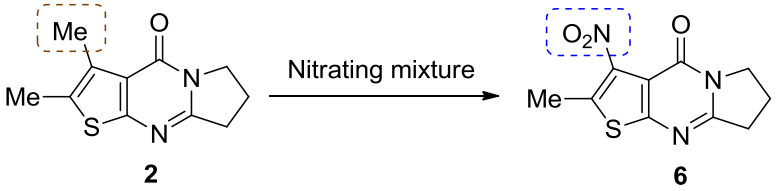
Table 1. Optimization of *ipso*-nitration reaction for the substrate **4**.



4 **6**

Entry	Catalyst/ (mol%)	Nitrate sources	Time (h)	Yeild (%)
1	$Cu(OAc)_2$/50	$AgNO_3$	5	65
2	$Cu(OAc)_2$/50	$NaNO_3$	5	45
3	$Cu(OAc)_2$/50	$Ca(NO_3)_2$	10	48
4	**$Cu(OAc)_2$/70**	**$AgNO_3$**	**10**	**85**
5	$Cu(OAc)_2$/70	$NaNO_3$	10	65
6	$Cu(OAc)_2$/70	$Ca(NO_3)_2$	10	62
7	$Cu(OAc)_2$/100	$AgNO_3$	15	85
8	$Cu(OAc)_2$/100	$NaNO_3$	15	68
9	$Cu(OAc)_2$/100	$Ca(NO_3)_2$	15	66
10	$Cu(OAc)_2$/60	$AgNO_3$	20	82

Table 2. Optimization of *ipso*-nitration reaction for the substrate **2**.



2 **6**

Entry	Nitrating mixture	Temperature (°C)/ Time (h)	Yield (%)
1	HNO_3/H_2SO_4	-10 – 0/5	—
2	HNO_3/CH_3COOH	-10 – 0/5	5
3	$Cu(NO_3)_2/ (CH_3CO)_2O$	-10 – 0/5	trace
4	$HNO_3/(CH_3CO)_2O$	-10 – 0/5	5
5	HNO_3	-25 – 10/2	15