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A novel synthesis of substituted 3-amino and 3-thio pyrimido[5,4-*e*]-1,2,4-triazine-5,7(1*H*,6*H*)-diones

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Abstract

Fervenulin is a natural product that has been extensively studied due to its molecular features and breadth of biological activities. Published studies have reported the generation of numerous analogues of the bicyclic pyrimidotriazinodione core. One underrepresented subclass are compounds with electron releasing atoms bonded directly to the C-3 position. We report an efficient and straightforward synthesis of compounds with substituted amino and thio functionality attached to the C-3 position. These are derived from a common 3-chloro precursor that is made in six steps in 15.8% overall yield from a starting chlorouracil. Our methodology should be applicable to the synthesis of C-3 ether congeners also, and through previously described chemistry be expandable to incorporating diversity at the *N*-6 position of the pyrimidotriazinodione core. The chemistry reported herein expands possibilities for the generation of diverse libraries of substituted pyrimidotriazinediones for future studies.

1 | INTRODUCTION

Fervenulin (1; Figure 1)[1] is a representative of naturally occurring 7-azapteridines (pyrimido[5,4-*e*][1,2,4]-triazines) isolated from cultures of *Streptomyces fervens*.[2] This class of heterocycles has been the subject of many synthetic studies[3] due to the breadth of its biological activities.[2,4] We have published studies on a novel approach to the synthesis of analogues of this class, leading to the generation of compounds with a variety of substituents at the C-3 and *N*-8 positions.[5] Several of these have been tested as small molecule antagonists of the oncogenic Tcf4/β-catenin protein complex, which is found at elevated levels in colorectal tumors.[6] Compound 2 is exemplary of one compound displaying good in vitro activity.

Because of the marked electron deficiency of the triazino ring, we were interested in truncated variants of 2 with electron releasing atoms bonded directly to the C-3 position (3; Figure 1). Literature examples of the pyrimidotriazinedione core of fervenulin adorned with such substituents are sparse with reports only for X = NH, NR[7], and O[7a,8]. This paper describes the development of an efficient and straightforward synthetic route to examples of 3, wherein X = NH, NR, and S, which are derived from a common precursor.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthesis of target compounds **9** and **10** is shown in Scheme 1 with bicyclic chlorotriazine **8** as a key intermediate. Prior routes to the synthesis of the *N*-8 methyl congener of **8** have been described,[8,9] but we found these to be unsatisfactory as we desired a generalized route that would permit the installation of variable alkyl and alkaryl substituents at both the *N*-6 and *N*-8 positions. Thus, we embarked on the route shown in Scheme 1. Cesium

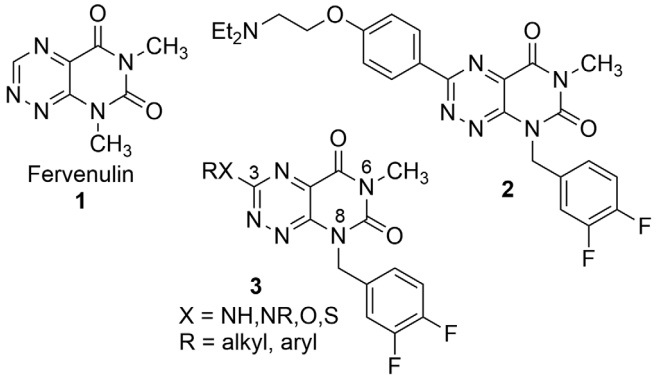
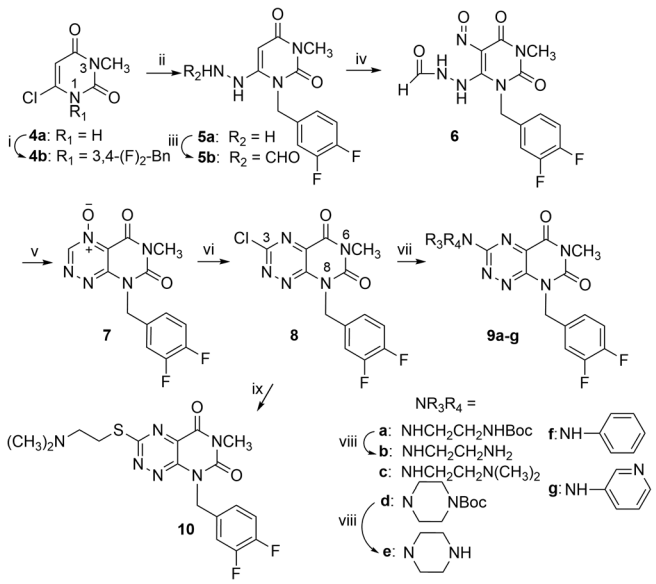


FIGURE 1 Fervenulin (**1**), β-catenin inhibitor (**2**) and target truncated analogues (**3**)



SCHEME 1 (i) 3,4-Difluorobenzyl bromide, Cs_2CO_3, DMF, rt, 5 h (82% yield); (ii) for **4b**: $NH_2NH_2 \cdot H_2O$, MeOH, 0°C—rt, 30 min (72% yield); (iii) AcOCHO, MeOH, rt, 50 min (69% yield); (iv) amyl nitrite, 1N aq. HCl, EtOH, rt, 2 h (73% yield); (v) HCO_2H, 100 °C, 1 h (73% yield); (vi) Vilsmeier reagent, 1,2-DCE, 50 °C, 2 h (73% yield); (vii) for **9a**, **9c**,**d**, **9f**: CH_3CN, rt to reflux, 30 min–4 days (57%–90% yield); for **9g**: 3-aminopyridine, $Pd(OAc)_2$, xantophos, K_2CO_3, *p*-dioxane, reflux, 2 h (78% yield); (viii) TMS triflate, 2,6-lutidine, DCM, rt, 1h (75 – 87% yield); (ix) $(CH_3)_2N(CH_2)_2SH \cdot HCl$, *i*-$Pr_2NEt$, DMF, 0 °C, 15 min (61% yield)

carbonate catalyzed alkylation of commercially available 6-chlorouracil **4a** with 3,4-difluorobenzyl bromide proceeded smoothly to give **4b** in 82% yield. Nucleophilic chloride displacement with excess hydrazine hydrate provided adduct **5a**, which was formylated with formic acetic anhydride to give formohydrazide **5b** in a 50% two-step yield. Acid-catalyzed nitrosation of **5b** with amyl nitrite gave **6** in 73% yield with the steps from **4b** to **6** following a prior generalized procedure.[10] Compound **6** was then ring-closed to bicyclic triazine *N*-oxide **7** in refluxing formic acid in 73% yield. The mechanism involves cyclization of **6** by nucleophilic attack of the nitroso nitrogen onto the carbonyl of the formylhydrazino moiety followed by dehydration as previously outlined.[8] Mild treatment of **7** with Vilsmeier reagent gave key intermediate **8** in 73% yield and an overall 15.8% in six steps from **4a**. Condensation of **8** with a range of commercially available amines in acetonitrile under variable conditions proceeded smoothly to provide **9a**, **9c**,**d**, and **9f** in 57%–90% yield with aniline adduct **9f** requiring reflux temperature and a 4-day reaction time.

Application of these conditions to 3-aminopyridine led to a complex reaction mixture without evidence of formation of **9g**. However, under Buchwald-Hartwig conditions (palladium[II] acetate, xantophos)[11] successful conversion to **9g** occurred in 78% yield. Adducts **9a** and **9d** were Boc-deprotected to **9b** and **9e**, respectively, under neutral conditions (trimethylsilyl triflate, 2,6-lutidine) in 75%–87% yield. A single example of a thiol adduct is shown in the amine-catalyzed addition of 2-(dimethylamino)ethanethiol to **8** in *N*,*N*-dimethylformamide at 0°C to give **10** in 61% yield. We believe these mild conditions should be applicable to a wide range of alkyl and aryl thiols.

We rigorously purified all compounds by conventional methods. Diagnostic peaks in NMR spectra (^1H and ^{13}C) along with mass spectrometry support the assigned structures.

3 | CONCLUSIONS

We have developed an efficient and straightforward synthetic route to representative examples of 3-(alkyl/aryl amino)- and 3-(alkylthio)-substituted 6,8-(dialkyl) pyrimido[5,4-*e*][1,2,4]triazine-5,7(6*H*,8*H*)-diones (**9** and **10**, respectively) derived from a common 3-chloro precursor **8**. Generalized conditions have been developed for chloride displacement with representative amine and sulfhydryl monomers, whereas electron-deficient aryl amines, such as 3-aminopyridine, required the application of Buchwald-Hartwig conditions for a successful reaction.

We did not investigate the reactions of **8** with alcohols to provide ether congeners **3** (X═O), but believe that these can be derived under conditions described previously for the *N*-8 methyl congener of **8**.[7a,8] Diversity at the *N*-6 position of **8** can be installed through previously described chemistry permitting the selective installation of alkyl and arylalkyl groups off the *N*-3 position of 6-chlorouracil.[6,12]

In summary, the chemistry reported herein expands possibilities for the generation of diverse libraries of

substituted pyrimido[5,4-*e*][1,2,4]triazine-5,7(6*H*,8*H*)-diones for future studies.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | Materials and methods

Materials and methods were employed as previously described.[13]

*6-Chloro-1-(3,4-difluorobenzyl)-3-methylpyrimidine-2,4(1H,3H)-dione (**4b**)*

A mixture of 6-chloro-3-methyluracil **(4a)** (5.0 g, 31.1 mmol), 3,4-difluorobenzyl bromide (4.78 ml, 37.38 mmol), cesium carbonate (15.2 g, 46.7 mmol), and *N*,*N*-dimethylformamide (30 ml) was stirred at room temperature for 5 h and then diluted with water (50 ml). The precipitated product was collected, washed with diethyl ether, and dried to leave **4b** (7.32 g, 82%) as a white solid: mp 105–106°C; ^{1}H NMR (chloroform-*d*): δ 7.21–7.11 (m, 3H, Ph-F_2 H-2, H-5, H-6), 5.99 (s, 1H, H-5), 5.23 (s, 2H, -CH_2Ph-F_2), 3.38 (s, 3H, NCH_3); MS *m/z* 287.0 (M + H).

*1-(3,4-Difluorobenzyl)-6-hydrazineyl-3-methylpyrimidine-2,4(1H,3H)-dione (**5a**)*

To a stirred suspension of **4b** (2.0 g, 6.98 mmol) in 10 ml methanol at 0°C was added slowly hydrazine monohydrate (3.7 ml). The mixture was brought to room temperature, stirred for 30 min, and concentrated to a residue that was diluted with dichloromethane. The solution was washed successively with 5% aqueous sodium carbonate and then brine, dried, and concentrated to leave 1.42 g (72%) of **5a** as a light yellow solid: mp 169–170°C; R_f 0.22 (dichloromethane: methanol 95: 5); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 8.11 (s, 1H, -N*H*NH_2), 7.4 (m, 1H, Ph-F_2 H-5), 7.25 m, 1H, Ph-F_2 H-2), 7.03 (t, 1H, Ph-F_2 H-6), 5.16 (s, 1H, H-5), 5.05 (s, 2H, -NHNH_2), 4.40 (s, 2H, -CH_2Ph-F_2), 3.12 (s, 3H, NCH_3); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 162.2, 155.8, 152.1, 134.6, 123.7, 118.0, 117.8, 116.5, 116.2, 74.6, 43.7, 27.6; MS *m/z* 283.0 (M + H).

N′*-(3-(3,4-Difluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)formohydrazide (**5b**)*

A mixture of formic acid and acetic anhydride (1:1 molar eq.) was heated at 50°C for 2 h. The solution was cooled and the formed formic acetic anhydride (2.5 ml, 32 mmol) was added to **5a** (4.5 g, 15.9 mmol) suspended in methanol (100 ml). The mixture was stirred for 50 min and then the precipitated product was collected by filtration, washed with methanol, and dried to leave 3.4 g (69%) of **5b** as a white solid: mp 208–211°C; R_f 0.35 (dichloromethane: methanol 95: 5); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 10.12, 9.80 (br s each, 1H, rotamers of-NHN*H*CHO), 9.11 (br s, 1H, -N*H*NHCHO), 8.15 (s, 1H, CHO), 7.45–7.25 (m, 2H, Ph-F_2 H-2, H-5), 7.15 (br s, 1H, Ph-F_2 H-6), 5.12 (s, 2H, -CH_2Ph-F_2), 4.90 (s, 1H, H-5), 3.12 (s, 3H, NCH_3); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 162.1, 160.9, 153.9, 151.7, 134.4, 124.2, 118.0, 117.8, 116.8, 116.6, 76.2, 44.5, 27.8; MS *m/z* 333.1 (M + Na).

*8-(3,4-Difluorobenzyl)-6-methyl-5,7-dioxo-5,6,7,8-tetrahydropyrimido[5,4-e][1,2,4]triazine-4-oxide (**7**)*

Compound **5b** (3 g, 9.67 mmol) was ground into a fine powder and suspended in ethanol (50 ml) at room temperature. Amyl nitrite (3.9 ml, 29 mmol) was added slowly to the mixture, followed by seven drops of 1 N aqueous HCl. The color of the solution changed from clear to red and an orange solid precipitated out. After stirring for 2 h, the precipitate (**6**) was collected, washed with ethanol, and dried under vacuum to yield 2.4 g (73%) of an orange solid. Multiple batches of **6** were combined and 10.05 g (29.6 mmol) was dissolved in formic acid (250 ml), and the solution was heated at 100°C for 1 h. The mixture was diluted with ethyl acetate and washed with water and brine. The combined aqueous layers were back extracted with ethyl acetate (2x), and the combined organic phases were dried and concentrated to a dark orange solid that was washed with water and then triturated in boiling 2-propanol. The solids were collected to give **7** (6.94 g, 73%) as a yellow solid: mp 182–183°C; R_f 0.74 (dichloromethane: methanol, 95: 5); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 9.53 (s, 1H, H-3), 7.48–7.35 (m, 2H, Ph-F_2 H-2, H-5), 7.29 (br s, 1H, Ph-F_2 H-6), 5.45 (s, 2H, -CH_2Ph-F_2), 3.26 (s, 3H, NCH_3); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 153.0, 151.0, 149.0, 148.5, 131.9, 126.0, 122.4, 118.8, 118.6, 117.5, 117.3, 45.8, 29.0; MS *m/z* 322.0 (M + H).

*3-Chloro-8-(3,4-difluorobenzyl)-6-methylpyrimido[5,4-e][1,2,4]triazine-5,7(6H,8H)-dione (**8**)*

A mixture of *N*,*N*-dimethylformamide (14.5 ml, 187 mmol), phosphorus oxychloride (1.74 ml, 18.7 mmol), and 1,2-dichloroethane (48 ml) was stirred at room temperature for 10 min. Compound **7** (3 g, 9.34 mmol) dissolved in 1,2-dichloroethane (45 ml) was added to the formed Vilsmeier reagent, and the solution was stirred at 50°C for 2 h. The mixture was cooled in an ice bath and carefully quenched with dropwise addition of water, followed by extraction with ethyl acetate (2x). The combined extracts were washed with water (2x), and then the combined aqueous washes were back extracted with ethyl acetate (2x). The combined organic phases

were dried and concentrated to a solid that was triturated in boiling 2-propanol to give **8** (2.31 g, 73%) as a yellow solid: mp 176–176.5°C; R_f 0.86 (dichloromethane: methanol, 95: 5); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.45–7.35 (m, 2H, Ph-F_2 H-2, H-5), 7.25 (s, 1H, Ph-F_2 H-6), 5.49 (s, 2H, -CH_2Ph-F_2), 3.36 (s, 3H, NCH_3); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 160.7, 157.9, 151.8, 149.2, 148.9, 132.4, 131.5, 118.9, 118.7, 117.7, 117.5, 45.3, 29.8; MS *m/z* 338.1 (M-H).

tert-*Butyl(2-((8-(3,4-difluorobenzyl)-6-methyl-5,7-dioxo-5,6,7,8.-tetrahydropyrimido[5,4-*e*][1,2,4]triazin-3-yl) amino)ethyl)carbamate (**9a**)*

A mixture of compound **8** (300 mg, 0.88 mmol), *N*-Boc-ethylenediamine (423 mg, 2.64 mmol), and acetonitrile (8 ml) was stirred at room temperature for 9 h and then concentrated. The residue was diluted with 5% aq. sodium bicarbonate and extracted with dichloromethane (3x). The combined organic phases were dried and concentrated to an oil that was dissolved in minimal 2-propanol for crystallization. The precipitate was collected, washed with 2-propanol, and dried to give **9a** (334 mg, 82%) as a yellow solid: mp 160–161°C; ^{1}H NMR (chloroform-*d*): δ 7.40 (m, 1H, Ph-F_2 H-5), 7.31 (s, 1H, Ph-F_2 H-6), 7.10 (q, 1H, Ph-F_2 H-2), 6.22 (br s, 1H, ArNH), 5.53 (s, 2H, -CH_2Ph-F_2), 4.86 (s, 1H, BocNH), 3.72 (m, 2H, ArNHCH_2-), 3.53 (s, 3H, NCH_3), 3.45 (m, 2H, BocNHCH_2-), 1.43 (s, 9H, Boc methyls); MS *m/z* 486.2 [M + H].

*3-([2-Aminoethyl]amino)-8-(3,4-difluorobenzyl)-6-methylpyrimido[5,4-*e*][1,2,4]triazine-5,7(6*H*,8*H*)-dione hydrochloride (**9b**)*

A room temperature solution of **9a** (150 mg, 0.32 mmol), 2,6-lutidine (347 mg, 3.2 mmol), and dichloromethane (10 ml) was treated with trimethylsilyl triflate (360 mg, 1.62 mmol) and the mixture was stirred for 1 h. Workup for **9a** left an oil that was dissolved in minimal 2-propanol. The addition of excess methanolic HCl resulted in the formation of a precipitate, which was collected, washed with 2-propanol, and dried to give **9b** hydrochloride (97 mg, 75%) as a yellow solid: mp 256°C dec.; NMR (dimethyl sulfoxide-d_6): δ 8.12 (s, 1H, ArNH), 8.03 (s, 3H, $H_3N^+CH_2$-), 7.42–7.33 (m, 2H, Ph-F_2 H-2, H-5), 7.27 (s, 1H, Ph-F_2 H-6), 5.41 (s, 2H, -CH_2Ph-F_2), 3.63 (dd, 2H, $H_3N^+CH_2$-), 3.34 (s, 3H, NCH_3), 3.04 (m, 2H, ArNHCH_2-); MS *m/z* 346.1 [M + H], 386.1 [M + Na].

*8-(3,**4**-Difluorobenzyl)-3-((2-(dimethylamino)ethyl) amino)-6-methylpyrimido[5,4-*e*][1,2,4]triazine-5,7 (6*H*,8*H*)-dione (**9c**)*

The reaction of **8** (100 mg, 0.29 mmol), *N*,*N*-dimethylethylenediamine (130 mg, 1.47 mmol), and acetonitrile (3 ml) was carried out for 30 min as described for **9a** to give **9c** (65 mg, 57%) as a red solid: mp 152–153°C; NMR (chloroform-*d*): δ 7.41 (m, 1H, Ph-F_2 H-5), 7.32 (s, 1H, Ph-F_2 H-6), 7.10 (q, 1H, Ph-F_2 H-2), 6.40 (s, 1H, ArNH), 5.53 (s, 2H, -CH_2Ph-F_2), 3.61 (d, 2H, ArNHCH_2-), 3.53 (s, 3H, NCH_3), 2.58 (t, 2H, CH_2N$(CH_3)_2$), 2.27 (s, 6H, -N$(CH_3)_2$); ^{13}C NMR (chloroform-*d*): δ 160.2, 149.1, 143.9, 132.8, 118.5, 118.3, 117.4, 117.3, 57.2, 45.0, 44.6, 39.1, 29.4; MS *m/z* 392.2 [M + H], 414.2 [M + Na]

tert-*Butyl 4-(8-(3,4-difluorobenzyl)-6-methyl-5,7-dioxo-5,6,7,8.-tetrahydropyrimido[5,4-*e*][1,2,4]triazin-3-yl) piperazine-1-carboxylate (**9d**)*

Reaction of **8** (300 mg, 0.88 mmol), *N*-Boc-piperazine (492 mg, 2.64 mmol), and acetonitrile (8 ml) was carried out as described for **9a** to give **9d** (390 mg, 90%): mp 160–161°C; ^{1}H NMR (chloroform-*d*): δ 7.40 (m, 1H, Ph-F_2 H-5), 7.30 (s, 1H, Ph-F_2 H-6), 7.10 (q, 1H, Ph-F_2 H-2), 5.53 (s, 2H, -CH_2Ph-F_2), 3.96 (m, 4H, ArN[CH_2-]$_2$), 3.57 (m, 4H, BocN[CH_2-]$_2$), 3.53 (s, 3H, NCH_3), 1.50 (s, 9H, Boc methyls); MS *m/z* 512.2 [M + Na].

*8-(3,4-Difluorobenzyl)-6-methyl-3-(piperazin-1-yl) pyrimido[5,4-*e*][1,2,4]triazine-5,7(6*H*,8*H*)-dione (**9e**)*

Reaction of **9d** (150 mg, 0.31 mmol), 2,6-lutidine (328 mg, 3.1 mmol), and dichloromethane (10 ml), and trimethylsilyl triflate (344 mg, 1.54 mmol) was carried out as described for **9b**, but without salt formation, to give **9e** (103 mg, 87%) as an orange solid following trituration in 2-propanol: mp 184°C; ^{1}H NMR (chloroform-*d*): δ 7.40 (m, 1H, Ph-F_2 H-5), 7.31 (s, 1H, Ph-F_2 H-6), 7.10 (q, 1H, Ph-F_2 H-2), 5.53 (s, 2H, -CH_2Ph-F_2), 3.95 (t, 4H, ArN[CH_2-]$_2$), 3.52 (s, 3H, NCH_3), 3.00 (t, 4H, HN[CH_2-]$_2$), 2.52 (s, 1H, NH); ^{13}C NMR (chloroform-*d*): δ 160.6, 160.2, 149.1, 143.1, 132.9, 131.5, 120.1, 118.4, 118.2, 117.4, 117.3, 45.8, 45.2, 44.6, 29.4; MS *m/z* 390.2 [M + H].

*8-(3,4-Difluorobenzyl)-6-methyl-3-(phenylamino) pyrimido[5,4-*e*][1,2,4]triazine-.5,7(6*H*,8*H*)-dione (**9f**)*

Reaction of **8** (100 mg, 0.29 mmol), aniline (270 µl, 2.9 mmol), and acetonitrile (2 ml) at reflux for 4 days was carried out as described for **9a** to give **9f** (85 mg, 73%) as a dark red solid: ^{1}H NMR (dimethyl sulfoxide –d_6): δ 10.46 (s, 1H, NH), 7.78 (d, J = 8.0 Hz, 2H, aniline *o*-H), 7.49–7.27 (m, 5H, aniline *m*-H, Ph-F_2 H-2, H-5, H-6), 7.01 (t, J = 7.3 Hz, 1H, aniline *p*-H), 5.45 (s, 2H, -CH_2Ph-F_2), 3.34 (s, 3H, NCH_3); MS *m/z* 397.2 (M + H).

*8-(3,4-Difluorobenzyl)-6-methyl-3-(pyridin-3-ylamino) pyrimido[5,4-*e*][1,2,4]triazine-5,7(6*H*,8*H*)-dione (**9g**)*

Following a previously described procedure,[11] a mixture of anhydrous *p*-dioxane (2 ml), xantphos (20.44 mg,

0.035 mmol), and palladium(II) acetate (3.97 mg, 0.018 mmol) was charged into flask #1 to generate the catalyst, and a mixture of **8** (60 mg, 0.177 mmol), 3-aminopyridine (16.62 mg, 0.177 mmol), potassium carbonate (488 mg, 3.53 mmol), and *p*-dioxane (2 ml) into flask #2. After transferring the solution of flask #1 to flask #2, the mixture was heated at reflux for 2 h. Workup as described for **9a** left a crude solid that was triturated in 2-propanol/dichloromethane and collected to give **9g** (55 mg, 78%) as a deep yellow solid: ^{1}H NMR (dimethyl sulfoxide-d_6) δ 10.70 (s, 1H, NH), 8.89 (s, 1H, pyr H-2), 8.21 (d, J = 12.5 Hz, 2H, pyr H-4, H-6), 7.49–7.27 (m, 4H, Ph-F_2 H-2, H-5, H-6, pyr H-5), 5.45 (s, 2H, -CH_2Ph-F_2), 3.33 (s, 3H, NCH_3); MS *m/z* 398.0 (M + H).

*8-(3,4-Difluorobenzyl)-3-((2-(dimethylamino)ethyl)thio)-6-methylpyrimido[5,4.-e][1,2,4]triazine-5,7(6H,8H)-dione (**10**)*

A mixture of **8** (150 mg, 0.44 mmol), 2-(dimethylamino) ethanethiol hydrochloride (187 mg, 1.32 mmol), *N*,*N*-diisopropylethylamine (153 µl, 0.88 mmol), and *N*,*N*-dimethylformamide (5 ml) was stirred in an ice bath for 15 min. The mixture was diluted with dichloromethane and washed with water (3x). Further workup as described for **9a** gave **10** (109 mg, 61%) as a yellow solid: mp 135–135.5°C; ^{1}H NMR (chloroform-*d*): δ 7.43 (t, 1H, Ph-F_2 H-5), 7.34 (s, 1H, Ph-F_2 H-6), 7.11 (q, 1H, Ph-F_2 H-2), 5.57 (s, 2H, -CH_2Ph-F_2), 3.54 (s, 3H, NCH_3), 3.45 (t, 2H, -CH_2SAr), 2.71 (t, 2H, -CH_2N$(CH_3)_2$), 2.33 (s, 6H, N$(CH_3)_2$); ^{13}C NMR (chloroform-*d*): δ 171.1, 159.0, 151.3, 149.1, 147.4, 132.1, 131.0, 118.7, 118.6, 117.6, 117.4, 57.8, 45.3, 44.8, 29.6, 29.2; MS *m/z* 409.1 [M + H].

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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