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Catalyst- and Additive-Free C(sp^3)−H Functionalization of (Thio)barbituric Acids *via* C-5 Dehydrogenative Aza-Coupling Under Ambient Conditions

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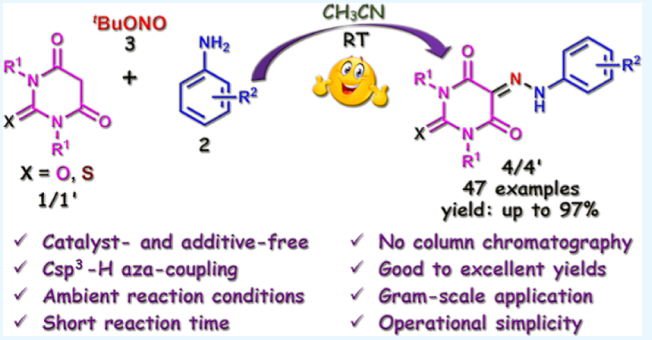
ABSTRACT: A one-pot room-temperature-based three-component reaction strategy has been accomplished to access a new series of bio-relevant barbituric/2-thiobarbituric acid hydrazones from the reaction between barbituric/2-thiobarbituric acids, primary aromatic amines, and *tert*-butyl nitrite in an acetonitrile solvent, without the aid of any catalysts/additives. The ambient reaction conditions can efficiently implement the C(sp^3)−H functionalization of barbituric/2-thiobarbituric acids *via* C-5 dehydrogenative aza-coupling. The process does not require column chromatographic purification; pure products are obtained by simple filtration of the resulting reaction mixture, followed by washing the crude residue with distilled water. The catalyst-free ambient reaction conditions, operational simplicity, broad substrate scope and tolerance for various functional groups, no need for chromatographic purification, good to excellent yields of products within reasonable reaction times in minutes, clean reaction profile, and gram-scale synthetic applicability make this procedure attractive, green, and cost-effective.



1. INTRODUCTION

Exploration of carbon−heteroatom bond-forming strategies always lies at the forefront of synthetic organic chemistry because this drives open new avenues for synthesizing functional organic molecules.[1] Amid various techniques for generating carbon−heteroatom bonds, C−H bond functionalization has recently emerged as promising in modern organic synthesis due to its inherent multifaceted advantages.[2] Still, many of these reported methodologies are associated with noticeable shortcomings simultaneously. On many occasions, they could not become devoid of the use of oxidants, costly and sensitive metal catalysts and additives, harmful organic solvents, tedious purification steps, and harsh reaction conditions.[3] Eventually, green chemistry-directed C−H functionalization for useful chemical transformations is of current choice among synthetic chemists. Among the C−H bond functionalizations, although C(sp^3)−H has recently been reported to emerge,[4] is still quite a challenging task, mainly due to the lack of activation and selectivity.[5]

As part of our ongoing endeavors in green chemistry-directed C−H functionalizations of useful organic scaffolds,[6] we thus felt pertinent in designing an efficient and practical C(sp^3)−H functionalization protocol to synthesize a series of diversely substituted barbituric/2-thiobarbituric hydrazones *via* C-5 dehydrogenative aza-coupling.[7] Substituted pyrimidines, categorically barbituric/2-thiobarbituric acids, act as building blocks for a handful of useful drugs with hypnotic, sedative, anticonvulsant, anaesthetic, antioxidant, antifungal, and central nervous system depressant activity.[8] The recent literature thus shows a considerable number of synthetic endeavors with barbituric/2-thiobarbituric acids yielding diverse series of functionalized barbituric/2-thiobarbituric acid derivatives with promising medicinal, pharmaceutical, and material properties.[9] Similarly, hydrazone derivatives also demonstrated their useful applicabilities as medicinal and pharmaceutical agents,[10] chemosensors,[11] linkers in preparing bifunctional molecules,[12] and ligands, directing groups, or auxiliaries in organic synthesis.[13] The new series of these molecules is thus anticipated to exhibit somewhat enhanced bioactivity and material properties.

We have recently developed a straightforward and practical synthetic method for a new series of diversely functionalized 5-(2-arylhydrazono)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (**4**)/5-(2-arylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones (**4′**) from a one-pot three-component reaction between

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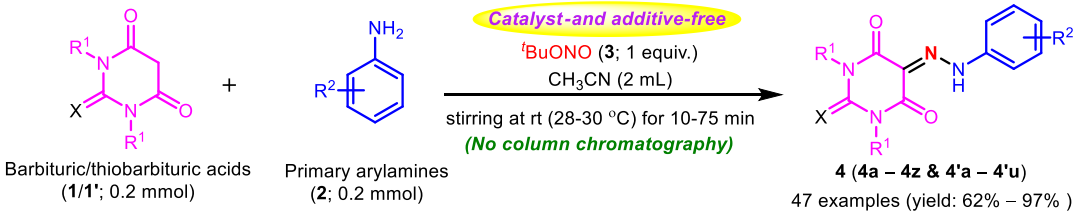
Scheme 1. Catalyst-Free C(sp^3)−H Functionalization of Barbituric/2-Thiobarbituric Acids *via* C-5 Dehydrogenative Aza-Coupling under Ambient Conditions



X = O, S; R^1 = H; CH_3; CH_2CH_3

R^2 = C_6H_5, 2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$SCH_3C_6H_4$, 4-$SCF_3C_6H_4$, 4-$OCF_3C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 2,5-di-ClC_6H_3, 3,5-di-$CF_3C_6H_3$, 4'-ClC_6H_4-4-O-C_6H_4

Table 1. Optimization of Reaction Conditions[a]

entry	solvent (2 mL)	N source (equiv)	condition	time (min)	yield (%)[b]
1		^{t}BuONO (1.0)	rt	25	63
2	H_2O	^{t}BuONO (1.0)	rt	30	41
3	EtOH	^{t}BuONO (1.0)	rt	60	47
4	EtOH/H_2O (1:1)	^{t}BuONO (1.0)	rt	45	34
5	DMSO	^{t}BuONO (1.0)	rt	60	73
6	1,4-dioxane	^{t}BuONO (1.0)	rt	45	78
7	DMF	^{t}BuONO (1.0)	rt	50	65
8	**CH_3CN**	**^{t}BuONO** (1.0)	**rt**	**15**	**93**
9	CH3CN/H_2O	^{t}BuONO (1.0)	rt	30	43
10	CH_3CN	^{t}BuONO (1.5)	rt	15	93
11	CH_3CN	^{t}BuONO (0.5)	rt	20	45
12	CH_3CN	$NaNO_2$ (1.0)	rt	120	49

[a]Reaction conditions: a mixture of barbituric acid (**1a**; 0.2 mmol) and aniline (**2a**; 0.2 mmol) was reacted either with TBN (in different proportions starting from 0.5 to 1.5 equiv) or sodium nitrite (1.0 equiv) in the absence or presence of various solvents (2 mL) without the aid of any catalysts and additives upon stirring at room temperature (28−30 °C); rt = room temperature. [b]Isolated yields.

barbituric acids (**1**)/2-thiobarbituric acids (**1′**), primary aromatic amines (**2**), and *tert*-butyl nitrite (TBN) (**3**) in an acetonitrile solvent under ambient conditions without the aid of any catalysts/additives (Scheme 1). The transformation involves C(sp^3)−H functionalization of barbituric/2-thiobarbituric acids to yield the hydrazone molecular hybrids *via* C-5 dehydrogenative aza-coupling. The present method is associated with several benefits such as operational simplicity, catalyst-free ambient reaction conditions, a broad substrate scope, avoidance of chromatographic purification, good to excellent yields, short reaction times, and gram-scale synthetic applicability. Recently, the development of catalyst-free and room-temperature-based synthetic methodologies is demanding due to their manifold advantages.[14]

2. RESULTS AND DISCUSSION

To arrive at the optimum reaction conditions for this dehydrogenative aza-coupling through C(sp^3)−H functionalization, we performed several trial reactions (Table 1, entries 1−11) with our model entry between unsubstituted barbituric acid (**1a**; 0.2 mmol), aniline (0.2 mmol), and TBN (varying amounts) targeting the desired product 5-(2-phenylhydrazono)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4a**) under ambient environments. As we perceived that the transformation might be implemented self-catalytically, we did not use any catalysts/additives. First, we checked the reaction under neat conditions and were delighted to isolate product **4a** in 63% yield (Table 1, entry 1) within 25 min. We then conducted a set of 10 more reactions using different solvent systems such as H_2O, EtOH, EtOH−H_2O (1:1), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), 1,4-dioxane, CH_3CN, and CH_3CN−H_2O (1:1) and also by varying the proportion of TBN starting from 0.5 to 1.5 equiv as the nitrating agent (Table 1, entries 2−11). We replaced TBN with sodium nitrite to check its relative nitrating performance (Table 1, entry 12). From these experimental outcomes, the best-suited reaction conditions for the model entry came out to be stirring the mixture of barbituric acid (**1a**; 0.2 mmol), aniline (0.2 mmol), and TBN (0.2 mmol; 1.0 equiv) dissolved in 2 mL of acetonitrile (CH_3CN) at room temperature (28−30 °C) to obtain **4a** in an excellent yield of 93% within 15 min (Table 1, entry 8). No tedious column chromatography was needed to purify compound **4a**, which was then characterized by the conventional spectroscopic [^{1}H NMR, ^{13}C NMR,

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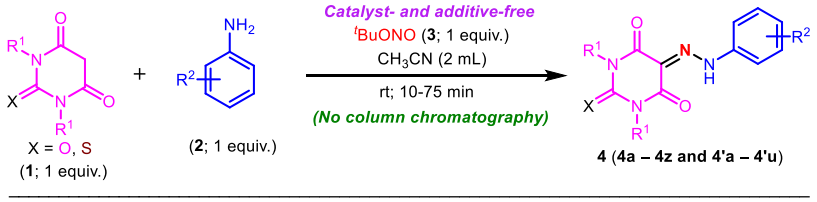
Table 2. Synthesis of Diversely Functionalized 5-(2-Arylhydrazono)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (4)[a] and 5-(2-Arylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones (4′)[a]



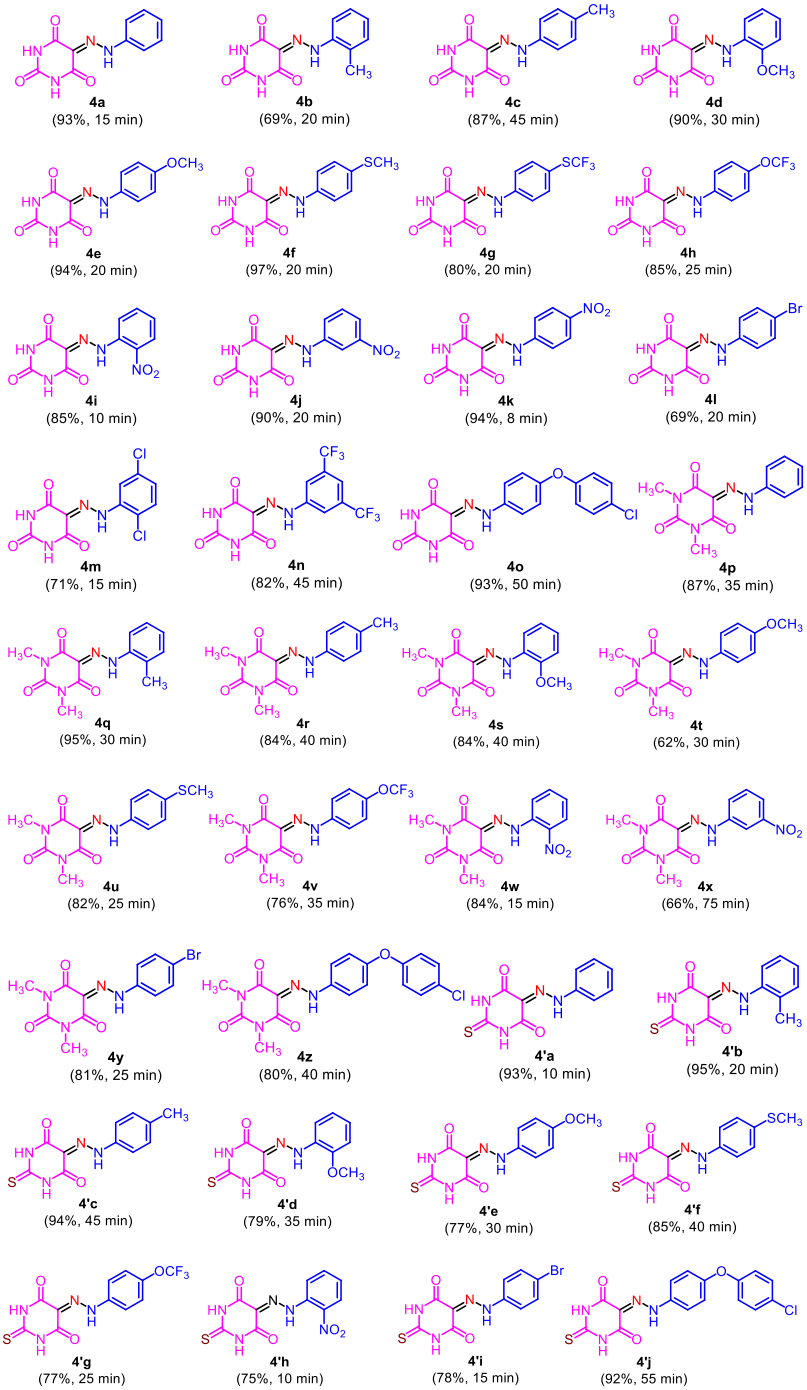


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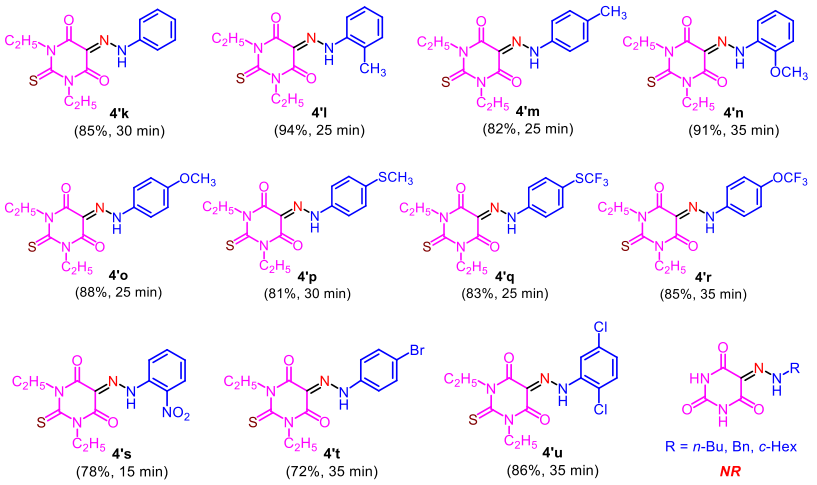
Table 2. continued



[a]Reaction conditions: a mixture of barbituric acid (**1**; 0.2 mmol)/2-thiobarbituric acids (**1′**; 0.2 mmol) and aromatic amines (**2**; 0.2 mmol) was reacted with TBN (0.2 mmol; 1.0 equiv) dissolved in 2 mL of acetonitrile upon stirring at room temperature (28−30 °C) in the absence of any catalysts and additives. Isolated yields; NR = no reaction.

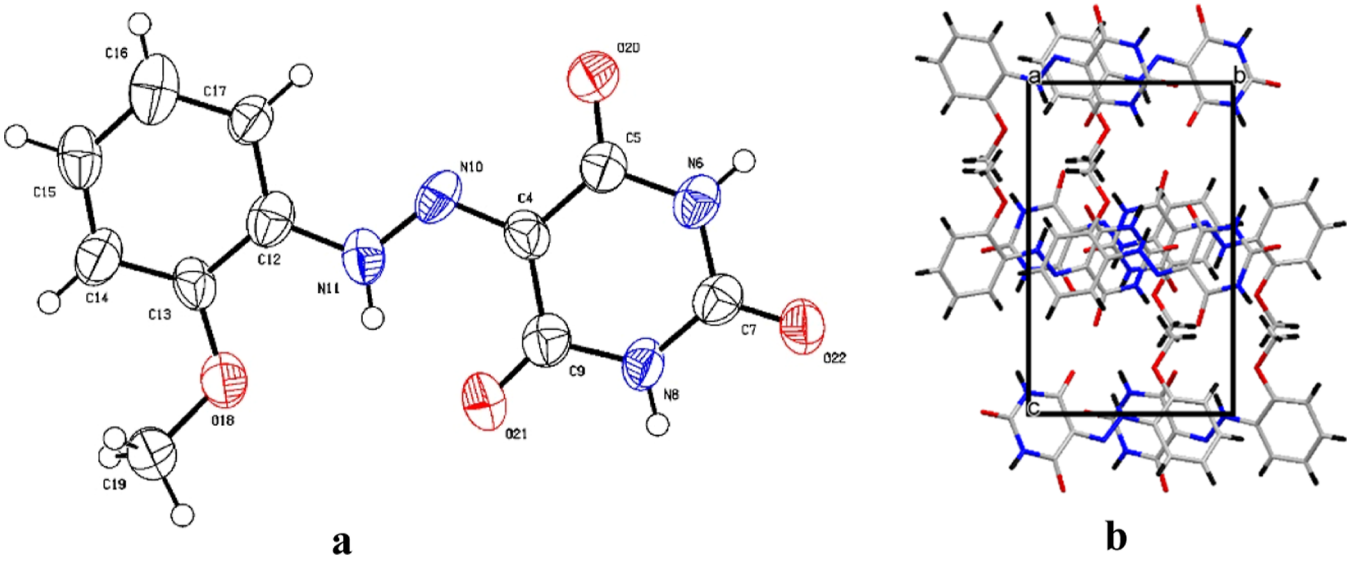


Figure 1. (a) ORTEP view of molecule **4d**, showing the atom-labeling scheme (displacement ellipsoids are drawn at the 50% probability level, and H atoms are shown as small spheres of arbitrary radii) and (b) packing arrangement of **4d** viewed along the *a*-axis.

distortionless enhancement by polarization transfer (DEPT-135), and high-resolution mass spectrometry (HRMS)] studies. Table 1 summarizes the overall results.

We then approached to validate the applicability of this newly developed protocol under the optimized reaction conditions. We performed a set of 14 different reactions from the mixture of barbituric acid (**1a**; 0.2 mmol), TBN (0.2 mmol), and diversely substituted primary aromatic amines (**2b−2o**; 0.2 mmol each) containing both electron-releasing and electron-withdrawing groups such as methyl, methoxyl, bromo, di-chloro, nitro, bis-trifluoromethyl, trifluoromethoxy, thiomethyl ($-SCH_3$), thiotrifluoromethyl ($-SCF_3$), 4-chlorophenoxy, and so forth. All these diverse substituents at the aromatic ring of anilines were found to be well-tolerated while implementing the transformations undergone in a facile manner, resulting in 5-(2-arylhydrazono)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones **4b−4o** in good to excellent yields ranging from 69 to 97% within 8−50 min (Table 2, compounds **4b-4o**). Another set of 11 more reactions were designed from the mixture of *N*,*N*-dimethylbarbituric acid (**1b**), TBN, and varying anilines under the optimized reaction conditions; all the reactions proceeded smoothly, giving rise to the desired products **4p−4z** in 62−95% with 15−75 min.

Encouraged by the experimental outcomes, we planned to extend the substrate scope by replacing barbituric acids with 2-thiobarbituric acids. Accordingly, we first checked the model entry by reacting 2-thiobarbituric acid (**1′a**; 0.2 mmol) with TBN (0.2 mmol) and aniline (**2a**; 0.2 mmol) in acetonitrile (2 mL) upon stirring at ambient conditions. As anticipated, we obtained the desired product, 5-(2-phenylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**4′a**) in 93% yield at 10 min (Table 2, compound **4′a**). We then performed a diverse range of 20 more reactions between thiobarbituric acid (**1′a**)/*N*,*N*-diethyl-2-thiobarbituric acid (**1′b**), TBN, and varying anilines under the optimized reaction conditions. To our delight, all these reactions proceeded smoothly, thereby

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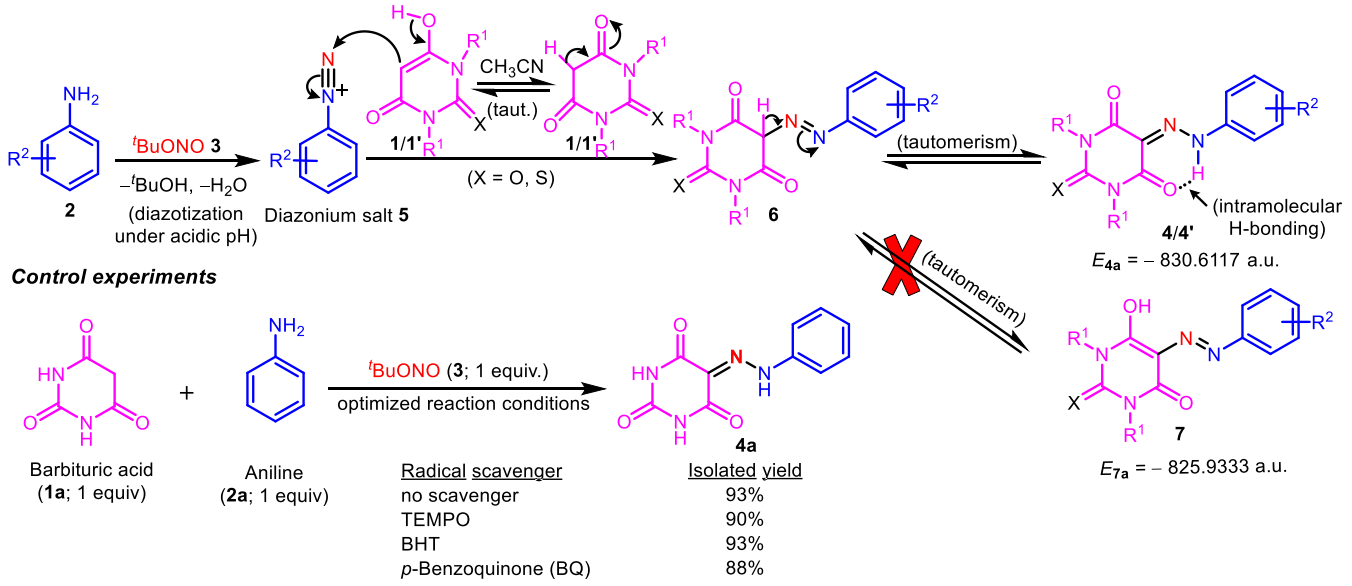
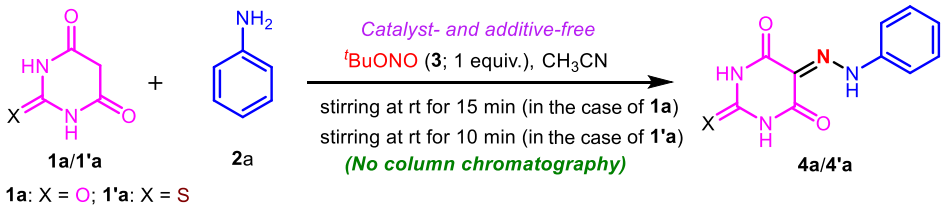
Scheme 2. Proposed Mechanism for the Catalyst-Free C(sp^3)−H Functionalization of Barbituric/2-Thiobarbituric Acids *via* C-5 Dehydrogenative Aza-Coupling under Ambient Conditions



Scheme 3. Representative Gram-Scale Experiments for Compounds 4a and 4′a



Reaction scale (solvent)	%Yield (Product **4a**)	%Yield (Product **4'a**)
1.0 mmol (10 mL)	94% (0.218 g)	92% (0.228 g)
5.0 mmol (20 mL)	91% (1.055 g)	90% (1.117 g)
10.0 mmol (30 mL)	91% (2.117 g)	90% (2.234 g)

affording the desired 5-(2-arylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones **4′b**−**4′u** with similar yields ranging from 72 to 95% within a reasonable time scale of 10−55 min (Table 2, products **4′b**−**4′u**). However, primary aliphatic amines (*viz.* *n*-butylamine, benzylamine, and *c*-hexylamine) did not give the desired product(s) as expected. Table 2 summarizes the overall results.

The synthesized products **4**/**4′** (**4a**−**4z** and **4′a**−**4′u**) were purified upon washing the crude products with distilled water (5 mL), followed by drying in the open air (see the Experimental Section). All the compounds were fully characterized based on their elemental analyses and detailed spectral studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for fluorine atom-containing molecules such as **4g**, **4h**, **4n**, **4v**, **4′g**, **4′q**, and **4′r**), and HRMS (for representative compounds **4a**, **4p**, **4′a**, and **4′k**). We obtained the 2D-NMR [correlation spectroscopy (COSY-45), heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond coherence (HMBC)] spectra for one representative compound (**4t**) to assign respective the ^{1}H and ^{13}C NMR data (see the Supporting Information). Further, we were also successful in developing suitable crystals for 5-(2-(2-methoxyphenyl)hydrazineylidene)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**4d**; Table 2), and its single-crystal X-ray analysis [CCDC 2170064; unit cell parameters: a = 25.717(6) Å, b = 7.9954(13) Å, c = 12.908(3) Å, α = 90.00°, β = 90.00°, γ = 90.00°, and *Pbcn*] documented in the present communication (see the Supporting Information) is in full structural agreement. The ORTEP and packing diagram of the molecule are represented in Figure 1.

TBN, a versatile chemical reagent, is well-regarded for diazotization reactions.[15] For our model reaction, we measured the pH to be 1.49 of the reaction mixture at the very beginning of the reaction. Hence, the transformation occurs under a highly acidic medium (self-catalysis). We thus herein propose a plausible mechanism (Scheme 2) for the catalyst-free C-5 dehydrogenative aza-coupling of barbituric/2-thiobarbituric acids (**1**/**1′**), leading to the synthesis of substituted 5-(2-arylhydrazono)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (**4**)/5-(2-arylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones (**4′**). The transformation begins with the formation of a diazonium salt **5** from the reaction between anilines **2** and TBN **3** under the reaction conditions. The electrophilic terminal azo-nitrogen of diazo-compound **5** is then attacked by the tautomeric form of barbituric/2-thiobarbituric acids (**1**/**1′**) through the nucleophilic C-5 position, thereby giving rise to adduct **6**. Intermediate **6** rapidly tautomerizes, following the path to yield **4**/**4′**, not **7**. We performed geometry optimization of the two possible structures, calculated at the DFT/B3LYP level along with the 6-31++G(d,p) basis set using Gaussion09 software.[16] The respective optimized energies were calculated to be −830.6117 and −825.9333 a.u.,

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respectively, thereby indicating more excellent thermodynamic stability of structure **4**/**4′**. The relatively greater stability of **4**/**4′** compared to that of **7** is attributed to intramolecular hydrogen bonding of type N−H···O present only within the structural skeleton **4**/**4′**. Further, the transformation proceeds through an ionic pathway that received experimental support when we observed that the conversion is not influenced by any radical scavengers (*viz.* (tetramethylpiperidin-1-yl)oxyl, butylated hydroxytoluene, and 1,4-benzoquinone). The proposed mechanism shows that water and *tert*-butanol are the green wastes in this transformation (Scheme 2).

Further, we checked the effectiveness of this catalyst- and additive-free protocol for larger-scale reactions using the model entries (Table 2, compounds **4a** and **4′a**) in 1.0, 5.0, and 10.0 millimolar scales (Scheme 3). The reactions proceeded satisfactorily in all the three larger scales, affording both the desired products **4a** and **4′a** with similar yields (90−94%) within almost the same time frame (10−15 min) compared to that in the lower sub-millimolar scale (see the Experimental Section).

3. CONCLUSIONS

In conclusion, we have developed a simple, straightforward, and efficient synthetic protocol for a new series of diversely functionalized 5-(2-arylhydrazono)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones (**4**)/5-(2-arylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones (**4′**) from a one-pot three-component reaction between barbituric acids (**1**)/2-thiobarbituric acids (**1′**), primary aromatic amines (**2**), and TBN (**3**) in an acetonitrile solvent, without the aid of any catalysts/additives, just under ambient conditions that are sufficient enough to implement the facile C(sp^3)−H functionalization of barbituric/2-thiobarbituric acids to furnish the hydrazone molecular hybrids *via* C-5 dehydrogenative aza-coupling. The process is devoid of any column chromatographic purification. The key advantages of this newly developed protocol are the operational simplicity, use of commercially available low-cost starting materials with a broader substrate scope, mild reaction conditions at room temperature, avoidance of catalysts/additives, clean reaction profile, excellent regioselectivity, good to excellent yields with short reaction times, no need for chromatographic purification, energy efficiency, and gram-scale synthetic applicability.

4. EXPERIMENTAL SECTION

4.1. General. All chemicals (analytical grade) were purchased from reputed companies and used without further purification. ^{1}H, ^{13}C, and ^{19}F NMR spectra were collected at 400 MHz, 100 MHz, and 376 MHz respectively, on a Bruker DRX spectrometer using DMSO-d_6 and $CDCl_3$ as the solvent. Chemical shifts were reported in δ (ppm), relative to the internal standard, tetramethylsilane. The signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants are reported as the *J* value in hertz. Structural assignments were determined with additional information from gCOSY, gHSQC, and gHMBC experiments. Elemental analyses were performed using a PerkinElmer 2400 Series II elemental analyzer instrument. MS was performed using a Bruker maXis Impact (Q-TOF) and a Microtek Q-TOF Micro YA 263 Waters high-resolution mass spectrometer. X-ray single crystallographic data were collected on an X′Calibur CCD area detector diffractometer (Agilent SuperNova SC-XRD). Melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} (Merck) plates.

4.2. General Procedure for the Synthesis of Substituted 5-(2-Arylhydrazono)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones (4) and 5-(2-Arylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones (4′). A magnetic stir bar, barbituric acids (**1**; 0.2 mmol)/2-thiobarbituric acids (**1′**; 0.2 mmol), primary aromatic amines (**2**; 0.2 mmol), TBN (**3**; 0.20 mmol), and 2 mL of acetonitrile were transferred to an oven-dried reaction vessel in a sequential manner. The reaction mixture was then stirred at ambient temperature (28−30 °C) for a stipulated time frame (10−75 min, monitored by TLC). On completion of the reaction, 2 mL of distilled water was added to the resulting mixture and shaken well for a while when the product started to precipitate. The precipitate was allowed to settle down and then filtered off using ordinary filter paper. The crude solid mass was thoroughly washed with 5 mL of distilled water, followed by drying in the open air to obtain pure products, 5-(2-arylhydrazono)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones **4** (**4a**−**4z**)/5-(2-arylhydrazono)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones **4′** (**4′a**−**4′u**). All the compounds were fully characterized based on their elemental analyses and detailed spectral studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **4g**, **4h**, **4n**, **4v**, **4′g**, **4′q**, and **4′r**), and HRMS (for **4a**, **4p**, **4′a**, and **4′k**). We obtained the 2D NMR (COSY-45, HMQC, and HMBC) spectra for one representative compound (**4t**) to assign the respective ^{1}H and ^{13}C NMR data (see the Supporting Information). Single X-ray crystallographic studies for a representative entry, 5-(2-(2-methoxyphenyl)hydrazono)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4d**; CCDC 2170064; see the Supporting Information), supported the structural skeleton deduced from detailed spectroscopic studies.

4.3. Gram-Scale Syntheses of Two Representative Compounds 4a and 4′a. A magnetic stir bar, barbituric acid (**1a**; 1.0 mmol, 0.128 g)/2-thiobarbituric acid (**1′a**; 1.0 mmol, 0.144 g), aniline (**2a**; 1.0 mmol, 0.093 g), TBN (**3**; 1.0 mmol, 0.115 g), and 10 mL of acetonitrile were transferred to an oven-dried round-bottom flask in a sequential manner. The reaction mixtures were then stirred at ambient temperature (28−30 °C) for 15 and 10 min (monitored by TLC), respectively. On completion of the reaction, 10 mL of distilled water was added to the resulting mixture and shaken well for a while when the product started to precipitate. The precipitate was allowed to settle down and filtered off using ordinary filter paper. The crude solid mass was thoroughly washed with 15 mL of distilled water, followed by drying in the open air to obtain the pure product. Upon drying, pure **4a** and **4′a** were isolated in 94% (0.218 g) and 92% (0.228 g) yields, respectively, and the physical and spectral properties (see the Supporting Information) of which were found to be similar to those obtained by the 0.2 mmol scale reaction. Further, two more gram-scale preparations (*viz.* 5 mmol and 10 mmol scale) were performed for both **4a** and **4′a** similarly. The mixtures of barbituric acid (**1a**; 5.0 mmol, 0.640 g/10.0 mmol, 1.281 g)/2-thiobarbituric acid (**1′a**; 5.0 mmol, 0.721 g/10.0 mmol, 1.441 g), aniline (**2a**; 5.0 mmol, 0.465 g/10.0 mmol, 0.931 g), TBN (**3**; 5.0 mmol, 0.575 g/10.0 mmol, 1.150 g), and 20 mL/30 mL of acetonitrile were reacted by stirring at ambient conditions, and the corresponding products were isolated upon standard workup in 91% (**4a**: 1.055 g in the 5 mmol scale and 2.117 g in

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the 10 mmol scale) and 90% (**4′a**: 1.117 g in the 5 mmol scale and 2.234 g in the 10 mmol scale) yields within the same time scale of 15 and 10 min, respectively.

4.4. Physical and Spectral Data of all the Synthesized Compounds 4 (4a−4z and 4′a−4′u). Physical and spectral data of all the synthesized compounds **4** (**4a−4z** and **4′a−4′u**) are given below.

*4.4.1. 5-(2-Phenylhydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4a**).* Straw yellow powder, yield: 93% (43 mg; 0.2 mmol scale), mp 298−299 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.14 (br s, 1H, −N*H*), 11.51 (br s, 1H, −N*H*), 11.29 (br s, 1H, −N*H*), 7.57 (d, 2H, J = 7.6 Hz, Ar-H), 7.47−7.43 (m, 2H, Ar-H), 7.26−7.22 (m, 1H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.30 (−NHCO−), 160.15 (−NHCO−), 149.99 (−NHCONH−), 141.42 (*C*), 129.88 (2× *C*H), 126.31 (*C*H), 117.83 (*C*), 116.81 (2× *C*H) ppm. HRMS (TOF MS ES$^+$): m/z 233.0675 [M + H]$^+$ calcd for $C_{10}H_8N_4O_3H$; found, 233.0676.

*4.4.2. 5-(2-(o-Tolyl)hydrazono)pyrimidine-2,4,6-(1H,3H,5H)-trione (**4b**).* Orange yellow powder, yield: 69% (34 mg; 0.2 mmol scale), mp 290−291 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.49 (br s, 1H, −N*H*), 11.59 (br s, 1H, −N*H*), 11.33 (br s, 1H, −N*H*), 7.67 (d, 1H, J = 8.0 Hz, Ar-H), 7.37−7.31 (m, 2H, Ar-H), 7.17 (t, 1H, J = 7.6 Hz, Ar-H), 2.35 (s, 3H, Ar-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.84 (−NHCO−), 159.85 (−NHCO−), 149.80 (−NHCONH−), 139.17 (*C*), 131.19 (*C*H), 127.63 (*C*H), 125.91 (*C*H), 125.61 (*C*), 118.51 (*C*), 114.70 (*C*H), 16.33 (Ar-CH_3) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.75. Found: C, 53.52; H, 4.13; N, 22.84.

*4.4.3. 5-(2-(p-Tolyl)hydrazono)pyrimidine-2,4,6-(1H,3H,5H)-trione (**4c**).* Yellow powder, yield: 87% (43 mg; 0.2 mmol scale), mp 297−298 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.19 (br s, 1H, −N*H*), 11.45 (br s, 1H, −N*H*), 11.23 (br s, 1H, −N*H*), 7.47 (d, 2H, J = 8.4 Hz, Ar-H), 7.26 (d, 2H, J = 8.4 Hz, Ar-H), 2.31 (s, 3H, Ar-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.19 (−NHCO−), 159.88 (−NHCO−), 149.79 (−NHCONH−), 139.03 (*C*), 135.68 (*C*), 130.10 (2× *C*H), 117.14 (*C*), 116.62 (2× *C*H), 20.53 (Ar-CH_3) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.75. Found: C, 53.79; H, 4.14; N, 22.63.

*4.4.4. 5-(2-(2-Methoxyphenyl)hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4d**).* Yellowish orange powder, yield: 90% (47 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.42 (s, 1H, −N*H*), 11.52 (s, 1H, −N*H*), 11.29 (s, 1H, −N*H*), 7.64 (d, 1H, J = 7.6 Hz, Ar-H), 7.25−7.18 (m, 2H, Ar-H), 7.10−7.07 (m, 1H, Ar-H), 3.94 (s, 3H, Ar-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.51 (−NHCO−), 159.89 (−NHCO−), 149.85 (−NHCONH−), 148.12 (*C*), 129.85 (*C*), 126.70 (*C*H), 121.67 (*C*H), 118.49 (*C*), 114.76 (*C*H), 112.15 (*C*H), 56.28 (Ar-OCH_3) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.47; H, 3.89; N, 21.49.

*4.4.5. 5-(2-(4-Methoxyphenyl)hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4e**).* Greenish yellow powder, yield: 94% (49 mg; 0.2 mmol scale), mp 294−295 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.29 (s, 1H, −N*H*), 11.43 (s, 1H, −N*H*), 11.22 (s, 1H, −N*H*), 7.53 (d, 2H, J = 9.2 Hz, Ar-H), 7.02 (d, 2H, J = 8.8 Hz, Ar-H), 3.76 (s, 3H, Ar-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.50 (−NHCO−), 160.46 (−NHCO−), 158.20 (*C*), 150.13 (−NHCONH−), 134.93 (*C*), 118.61 (2× *C*H), 116.66 (*C*), 115.23 (2× *C*H), 55.74 (Ar-OCH_3) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.52; H, 3.79; N, 21.49.

*4.4.6. 5-(2-(4-(Methylthio)phenyl)hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4f**).* Brownish yellow powder, yield: 97% (54 mg; 0.2 mmol scale), mp 299−301 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.18 (s, 1H, −N*H*), 11.49 (s, 1H, −N*H*), 11.27 (s, 1H, −N*H*), 7.53 (d, 2H, J = 8.4 Hz, Ar-H), 7.33 (d, 2H, J = 8.8 Hz, Ar-H), 2.48 (s, 3H, Ar-SCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.33 (−NHCO−), 160.19 (−NHCO−), 150.02 (−NHCONH−), 138.77 (*C*), 136.27 (*C*), 127.22 (2× *C*H), 117.56 (2× *C*H), 117.49 (*C*), 15.04 (Ar-SCH_3) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.62; N, 20.13. Found: C, 47.62; H, 3.57; N, 20.22.

*4.4.7. 5-(2-(4-((Trifluoromethyl)thio)phenyl)hydrazono)-pyrimidine-2,4,6(1H,3H,5H)-trione (**4g**).* Deep yellow powder, yield: 80% (53 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.98 (br s, 1H, −N*H*), 11.59 (br s, 1H, −N*H*), 11.37 (br s, 1H, −N*H*), 7.78 (d, 2H, J = 8.8 Hz, Ar-H), 7.71 (d, 2H, J = 8.8 Hz, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.76 (−NHCO−), 159.66 (−NHCO−), 149.79 (−NHCONH−), 144.17 (*C*), 137.88 (2× *C*H), 129.57 (−SCF_3, J_{CF}^1 = 307 Hz), 119.42 (*C*), 118.68 (*C*), 117.68 (2× *C*H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ −42.53 ppm. Elemental Anal. Calcd (%) for $C_{11}H_7F_3N_4O_3S$: C, 39.76; H, 2.12; N, 16.86. Found: C, 39.59; H, 2.07; N, 16.91.

*4.4.8. 5-(2-(4-(Trifluoromethoxy)phenyl)hydrazono)-pyrimidine-2,4,6(1H,3H,5H)-trione (**4h**).* Greenish yellow powder, yield: 85% (54 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.04 (br s, 1H, −N*H*), 11.52 (br s, 1H, −N*H*), 11.33 (br s, 1H, −N*H*), 7.71 (d, 2H, J = 8.8 Hz, Ar-H), 7.46 (d, 2H, J = 8.4 Hz, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.87 (−NHCO−), 159.81 (−NHCO−), 149.80 (−NHCONH−), 145.58 (*C*), 140.63 (*C*), 122.47 (2× *C*H), 120.08 (−OCF_3, J_{CF}^1 = 254 Hz), 118.48 (*C*), 118.19 (2× *C*H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ −57.02 ppm. Elemental Anal. Calcd (%) for $C_{11}H_7F_3N_4O_4$: C, 41.78; H, 2.23; N, 17.72. Found: C, 41.81; H, 2.18; N, 17.87.

*4.4.9. 5-(2-(2-Nitrophenyl)hydrazono)pyrimidine-2,4,6-(1H,3H,5H)-trione (**4i**).* Yellow powder, yield: 85% (47 mg; 0.2 mmol scale), mp 278−279 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 15.19 (s, 1H, −N*H*), 11.74 (s, 1H, −N*H*), 11.51 (s, 1H, −N*H*), 8.26 (d, 1H, J = 8.4 Hz, Ar-H), 8.09 (d, 1H, J = 8.4 Hz, Ar-H), 7.89−7.86 (m, 1H, Ar-H), 7.40−7.36 (m, 1H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.57 (−NHCO−), 159.71 (−NHCO−), 149.93 (−NHCONH−), 137.67 (*C*), 136.78 (*C*H), 135.62 (*C*), 126.21 (*C*H), 124.98 (*C*H), 122.31 (*C*), 117.33 (*C*H) ppm. Elemental Anal. Calcd (%) for $C_{10}H_7N_5O_5$: C, 43.33; H, 2.55; N, 25.27. Found: C, 43.46; H, 2.61; N, 25.41.

*4.4.10. 5-(2-(3-Nitrophenyl)hydrazono)pyrimidine-2,4,6-(1H,3H,5H)-trione (**4j**).* Mustard yellow powder, yield: 90% (50 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.99 (br s, 1H, −N*H*), 11.59 (br s, 1H, −N*H*), 11.39 (s, 1H, −N*H*), 8.44 (s, 1H, Ar-H), 8.03 (d, 2H, J = 8.0 Hz, Ar-H), 7.73−7.69 (m, 1H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.57 (−NHCO−), 159.67 (−NHCO−), 149.78 (−NHCONH−), 148.66 (*C*), 142.99

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(*C*), 131.01 (*C*H), 122.89 (*C*H), 119.65 (*C*H), 119.45 (*C*), 110.95 (*C*H) ppm. Elemental Anal. Calcd (%) for $C_{10}H_7N_5O_5$: C, 43.33; H, 2.55; N, 25.27. Found: C, 43.18; H, 2.62; N, 25.18.

*4.4.11. 5-(2-(4-Nitrophenyl)hydrazono)pyrimidine-2,4,6-(1H,3H,5H)-trione (**4k**).* Yellow powder, yield: 94% (52 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H, −N*H*), 8.29 (d, 2H, *J* = 9.2 Hz, Ar-H), 7.76 (d, 2H, *J* = 9.2 Hz, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.75 (−NHCO−), 159.74 (−NHCO−), 149.92 (−NHCONH−), 147.06(*C*), 143.99 (*C*), 125.77 (2× *C*H), 120.88 (*C*), 116.87 (2× *C*H) ppm. Elemental Anal. Calcd (%) for $C_{10}H_7N_5O_5$: C, 43.33; H, 2.55; N, 25.27. Found: C, 43.48; H, 2.49; N, 25.39.

*4.4.12. 5-(2-(4-Bromophenyl)hydrazono)pyrimidine-2,4,6-(1H,3H,5H)-trione (**4l**).* Pale yellow powder, yield: 69% (43 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.03 (br s, 1H, −N*H*), 11.54 (br s, 1H, −N*H*), 11.33 (br s, 1H, −N*H*), 7.63 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.54 (d, 2H, *J* = 9.2 Hz, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.12 (−NHCO−), 160.06 (−NHCO−), 149.99 (−NHCONH−), 140.95 (*C*), 132.64 (2× *C*H), 118.81 (2× *C*H), 118.42 (*C*), 118.18 (*C*) ppm. Elemental Anal. Calcd (%) for $C_{10}H_7BrN_4O_3C$, 38.61; H, 2.27; N, 18.01. Found: C, 38.49; H, 2.33; N, 18.19.

*4.4.13. 5-(2-(2,5-Dichlorophenyl)hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4m**).* Golden yellow powder, yield: 71% (43 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.36 (br s, 1H, −N*H*), 11.77 (br s, 1H, −N*H*), 11.51 (br s, 1H, −N*H*), 7.68 (d, 1H, *J* = 2.4 Hz, Ar-H), 7.64 (d, 1H, *J* = 8.8 Hz, Ar-H), 7.30 (dd, 1H, *J* = 8.4 and 2.4 Hz, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.48 (−NHCO−), 159.35 (−NHCO−), 149.67 (−NHCONH−), 138.83 (*C*), 133.39 (*C*), 131.56 (*C*H), 125.69 (*C*H), 121.32 (*C*), 119.13 (*C*), 115.33 (*C*H) ppm. Elemental Anal. Calcd (%) for $C_{10}H_6Cl_2N_4O_3$. C, 39.89; H, 2.01; N, 18.61. Found: C, 39.71; H, 2.07; N, 18.49.

*4.4.14. 5-(2-(3,5-Bis(trifluoromethyl)phenyl)hydrazono)-pyrimidine-2,4,6(1H,3H,5H)-trione (**4n**).* Bright yellow powder, yield: 82% (60 mg; 0.2 mmol scale), mp 289−290 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.96 (br s, 1H, −N*H*), 11.65 (br s, 1H, −N*H*), 11.46 (s, 1H, −N*H*), 8.26 (s, 2H, Ar-H), 7.86 (s, 1H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 161.62 (−NHCO−), 160.08 (−NHCO−), 150.02 (−NHCONH−), 143.97 (*C*), 132.25−131.25 (m, 2*C*), 123.32 (2× *C*F$_3$, J_{CF}^{1} = 271 Hz), 120.32 (*C*), 118.15 (*C*H), 117.20 (2× *C*H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ −61.64. Elemental Anal. Calcd (%) for $C_{12}H_6F_6N_4O_3$. C, 39.14; H, 1.64; N, 15.22. Found: C, 39.27; H, 1.51; N, 15.34.

*4.4.15. 5-(2-(4-(4-Chlorophenoxy)phenyl)hydrazono)-pyrimidine-2,4,6(1H,3H,5H)-trione (**4o**).* Greenish yellow powder, yield: 93% (67 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.18 (br s, 1H, −N*H*), 11.48 (br s, 1H, −N*H*), 11.28 (br s, 1H, −N*H*), 7.62−7.44 (m, 4H, Ar-H), 7.09 (br s, 4H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 162.08 (−NHCO−), 159.88 (−NHCO−), 155.57 (*C*), 154.27 (*C*), 149.82 (−NHCONH−), 137.49 (*C*), 129.97 (2× *C*H), 127.39 (*C*), 120.27 (2× *C*H), 119.96 (2× *C*H), 118.53 (2× *C*H), 117.42 (*C*) ppm. Elemental Anal. Calcd (%) for $C_{16}H_{11}ClN_4O_4$: C, 53.57; H, 3.09; N, 15.62. Found: C, 53.71; H, 3.14; N, 15.51.

*4.4.16. 1,3-Dimethyl-5-(2-phenylhydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4p**).* Yellow powder, yield: 87% (45 mg; 0.2 mmol scale), mp 266−267 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.64 (br s, 1H, −N*H*), 7.57−7.55 (m, 2H, Ar-H), 7.46−7.42 (m, 2H, Ar-H), 7.29−7.26 (m, 1H, Ar-H), 3.43 (s, 3H, −NC*H*$_3$), 3.39 (s, 3H, −NC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.31 (−N(CH$_3$)*C*O−), 159.26 (−N(CH$_3$)*C*O−), 150.85 (*C*O(N−CH$_3$)$_2$), 140.88 (*C*), 129.88 (2× *C*H), 127.39 (*C*H), 117.40 (2× *C*H), 116.46 (*C*), 28.71 (−NCH$_3$), 27.62 (−NCH$_3$) ppm. HRMS (TOF MS ES$^+$): *m*/*z* 261.0982 [M + H]$^+$ calcd for $C_{12}H_{12}N_4O_3H$; found, 261.0976; *m*/*z* 283.0802 [M + Na]$^+$ calcd for $C_{12}H_{12}N_4O_3Na$; found, 283.0794.

*4.4.17. 1,3-Dimethyl-5-(2-(o-tolyl)hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4q**).* Yellow powder, yield: 95% (52 mg; 0.2 mmol scale), mp 251−252 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.83 (br s, 1H, −N*H*), 7.94 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.31 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.23−7.16 (m, 2H, Ar-H), 3.43 (s, 3H, −NC*H*$_3$), 3.39 (s, 3H, −NC*H*$_3$), 2.45 (s, 3H, Ar-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.43 (−N(CH$_3$)*C*O−), 159.32 (−N(CH$_3$)*C*O−), 150.84 (*C*O(N−CH$_3$)$_2$), 139.14 (*C*), 131.15 (*C*H), 127.89 (*C*H), 127.15 (*C*H), 126.38 (*C*), 117.00 (*C*), 116.49 (*C*H), 28.70 (−NCH$_3$), 27.63 (−NCH$_3$), 17.05 (Ar-CH$_3$) ppm. Elemental Anal. Calcd (%) for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.77; H, 5.19; N, 20.34.

*4.4.18. 1,3-Dimethyl-5-(2-(p-tolyl)hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4r**).* Yellow powder, yield: 87% (45 mg; 0.2 mmol scale), mp 244−245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.67 (br s, 1H, −N*H*), 7.45 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.23 (d, 2H, *J* = 8.4 Hz, Ar-H), 3.41 (s, 3H, −NC*H*$_3$), 3.37 (s, 3H, −NC*H*$_3$), 2.37 (s, 3H, Ar-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.32 (−N(CH$_3$)*C*O−), 159.35 (−N(CH$_3$)*C*O−), 150.88 (*C*O(N−CH$_3$)$_2$), 138.59 (*C*), 137.70 (*C*), 130.42 (2× *C*H), 117.34 (2× *C*H), 115.97 (*C*), 28.64 (−NCH$_3$), 27.55 (−NCH$_3$), 21.25 (Ar-CH$_3$) ppm. Elemental Anal. Calcd (%) for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.78; H, 5.09; N, 20.36.

*4.4.19. 5-(2-(2-Methoxyphenyl)hydrazono)-1,3-dimethyl-pyrimidine-2,4,6(1H,3H,5H)-trione (**4s**).* Orange yellow powder, yield: 95% (52 mg; 0.2 mmol scale), mp 220−222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.73 (br s, 1H, −N*H*), 7.93 (dd, 1H, *J* = 8.0 and 1.2 Hz, Ar-H), 7.24−7.19 (m, 1H, Ar-H), 7.04 (t, 1H, *J* = 7.6 Hz, Ar-H), 6.96 (d, 1H, *J* = 8.4 Hz, Ar-H), 3.98 (s, 3H, Ar-OC*H*$_3$) 3.41 (s, 3H, −NC*H*$_3$), 3.38 (s, 3H, −NC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.97 (2*C*), 159.51 (−N(CH$_3$)*C*O−), 150.92 (*C*O(N−CH$_3$)$_2$), 149.10 (*C*), 130.08 (*C*), 127.77 (*C*H), 121.86 (*C*H), 116.76 (*C*H), 111.20 (*C*H), 56.20 (Ar-OCH$_3$), 28.63 (−NCH$_3$), 27.59 (−NCH$_3$) ppm. Elemental Anal. Calcd (%) for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.84; H, 4.79; N, 19.18.

*4.4.20. 5-(2-(4-Methoxyphenyl)hydrazono)-1,3-dimethyl-pyrimidine-2,4,6(1H,3H,5H)-trione (**4t**).* Yellow powder, yield: 62% (36 mg; 0.2 mmol scale), mp 211−212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.77 (br s, 1H, −N*H*), 7.49 (d, 2H, *J* = 9.2 Hz, Ar-H), 6.94 (d, 2H, *J* = 9.2 Hz, Ar-H), 3.82 (s, 3H, Ar-OC*H*$_3$), 3.39 (s, 3H, −NC*H*$_3$), 3.36 (s, 3H, −NC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.37 (−N(CH$_3$)*C*O−), 159.44 (−N(CH$_3$)*C*O−), 159.20 (*C*), 150.89 (*C*O(N−CH$_3$)$_2$), 134.40 (*C*), 118.86 (2× *C*H), 115.58 (*C*), 115.10 (2× *C*H), 55.74 (Ar-OCH$_3$), 28.58 (−NCH$_3$), 27.49 (−NCH$_3$) ppm. Elemental Anal. Calcd (%) for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.68; H, 4.77; N, 19.21.

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*4.4.21. 1,3-Dimethyl-5-(2-(4-(methylthio)phenyl)-hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4u**).* Orange powder, yield: 82% (50 mg; 0.2 mmol scale), mp 220−222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.68 (br s, 1H, −N*H*), 7.48 (d, 2H, J = 8.4 Hz, Ar-H), 7.28 (d, 2H, J = 8.8 Hz, Ar-H), 3.41 (s, 3H, −NCH_3), 3.37 (s, 3H, −NCH_3), 2.50 (s, 3H, Ar-SCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.33 (−N(CH_3)*C*O−), 159.25 (−N(CH_3)*C*O−), 150.81 (*C*O(N−CH_3)$_2$), 138.35 (*C*), 138.19 (*C*), 127.51 (2× *C*H), 117.84 (2× *C*H), 116.20 (*C*), 28.68 (−NCH_3), 27.59 (−NCH_3), 15.95 (Ar-SCH_3) ppm. Elemental Anal. Calcd (%) for $C_{13}H_{14}N_4O_3S$: C, 50.97; H, 4.61; N, 18.29. Found: C, 50.89; H, 4.68; N, 18.37.

*4.4.22. 1,3-Dimethyl-5-(2-(4-(trifluoromethoxy)phenyl)-hydrazono)pyrimidine-2,4,6(1H,3H,5H)-trione (**4v**).* Bright yellow powder, yield: 76% (52 mg; 0.2 mmol scale), mp 174−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.61 (br s, 1H, −N*H*), 7.58 (d, 2H, J = 8.8 Hz, Ar-H), 7.29 (d, 2H, J = 8.8 Hz, Ar-H), 3.42 (s, 3H, −NCH_3), 3.39 (s, 3H, −NCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.25 (−N(CH_3)*C*O−), 159.04 (−N(CH_3)*C*O−), 150.69 (*C*O(N−CH_3)$_2$), 147.70 (*C*), 139.39 (*C*), 122.59 (2× *C*H), 120.52 (−OCF_3, J_{CF}^1 = 257 Hz), 118.47 (2× *C*H), 117.01 (*C*), 28.78 (−NCH_3), 27.70 (−NCH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.03 ppm. Elemental Anal. Calcd (%) for $C_{13}H_{11}F_3N_4O_4$: C, 45.36; H, 3.22; N, 16.28. Found: C, 45.23; H, 3.19; N, 16.39.

*4.4.23. 1,3-Dimethyl-5-(2-(2-nitrophenyl)hydrazono)-pyrimidine-2,4,6(1H,3H,5H)-trione (**4w**).* Yellow powder, yield: 84% (51 mg; 0.2 mmol scale), mp 260−262 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 15.24 (s, 1H, −N*H*), 8.29 (d, 1H, J = 7.6 Hz, Ar-H), 8.11 (d, 1H, J = 8.0 Hz, Ar-H), 7.92 (t, 1H, J = 7.6 Hz, Ar-H), 7.42 (t, 1H, J = 7.6 Hz, Ar-H), 3.24 (s, 6H, 2× −NCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 159.86 (−N(CH_3)*C*O−), 158.31 (−N(CH_3)*C*O−), 150.48 (*C*O(N−CH_3)$_2$), 137.38 (*C*), 136.65 (*C*H), 135.63 (*C*), 126.08 (*C*H), 125.00 (*C*H), 121.45 (*C*), 117.20 (*C*H), 28.31 (−NCH_3), 27.49 (−NCH_3) ppm. Elemental Anal. Calcd (%) for $C_{12}H_{11}N_5O_5$: C, 47.22; H, 3.63; N, 22.94. Found: C, 47.08; H, 3.69; N, 22.82.

*4.4.24. 1,3-Dimethyl-5-(2-(3-nitrophenyl)hydrazono)-pyrimidine-2,4,6(1H,3H,5H)-trione (**4x**).* Yellow powder, yield: 66% (40 mg; 0.2 mmol scale), mp 228−230 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.03 (br s, 1H, -N*H*), 8.51−8.50 (m, 1H, Ar-H), 8.09−8.04 (m, 2H, Ar-H), 7.76−7.72 (m, 1H, Ar-H), 3.23 (s, 3H, −NCH_3), 3.22 (s, 3H, −NCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 159.89 (−N(CH_3)*C*O−), 158.56 (−N(CH_3)*C*O−), 150.60 (*C*O(N−CH_3)$_2$), 148.67 (*C*), 143.02 (*C*), 131.06 (*C*H), 123.03 (*C*H), 119.85 (*C*H), 118.88 (*C*), 111.21 (*C*H), 28.21 (−NCH_3), 27.30 (−NCH_3) ppm. Elemental Anal. Calcd (%) for $C_{12}H_{11}N_5O_5$: C, 47.22; H, 3.63; N, 22.94. Found: C, 47.38; H, 3.70; N, 22.85.

*4.4.25. 5-(2-(4-Bromophenyl)hydrazono)-1,3-dimethyl-pyrimidine-2,4,6(1H,3H,5H)-trione (**4y**).* Yellow powder, yield: 81% (55 mg; 0.2 mmol scale), mp 278−280 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.57 (br s, 1H, −N*H*), 7.55 (d, 2H, J = 8.8 Hz, Ar-H), 7.43 (d, 2H, J = 8.8 Hz, Ar-H), 3.42 (s, 3H, −NCH_3), 3.38 (s, 3H, −NCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.26 (−N(CH_3)*C*O−), 159.04 (−N(CH_3)*C*O−), 150.70 (*C*O(N−CH_3)$_2$), 139.93 (*C*), 132.94 (2× *C*H), 120.46 (*C*), 118.72 (2× *C*H), 116.87 (*C*), 28.76 (−NCH_3), 27.69 (−NCH_3) ppm. Elemental Anal. Calcd (%) for $C_{12}H_{11}BrN_4O_3$: C, 42.50; H, 3.27; N, 16.52. Found: C, 42.63; H, 3.24; N, 16.43.

*4.4.26. 5-(2-(4-(4-Chlorophenoxy)phenyl)hydrazono)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**4z**).* Yellow powder, yield: 80% (62 mg; 0.2 mmol scale), mp 202−203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.73 (br s, 1H, −N*H*), 7.54 (d, 2H, J = 8.4 Hz, Ar-H), 7.32 (d, 2H, J = 8.4 Hz, Ar-H), 7.05 (d, 2H, J = 8.4 Hz, Ar-H), 6.96 (d, 2H, J = 8.4 Hz, Ar-H), 3.42 (s, 3H, −NCH_3), 3.38 (s, 3H, −NCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.38 (−N(CH_3)*C*O−), 159.29 (−N(CH_3)*C*O−), 156.37 (*C*), 155.43 (*C*), 150.84 (*C*O(N−CH_3)$_2$), 136.64 (*C*), 130.09 (2× *C*H), 129.12 (*C*), 120.48 (2× *C*H), 119.90 (2× *C*H), 118.98 (2× *C*H), 116.27 (*C*), 28.71 (−NCH_3), 27.62 (−NCH_3) ppm. Elemental Anal. Calcd (%) for $C_{18}H_{15}ClN_4O_4$: C, 55.89; H, 3.91; N, 14.49. Found: C, 55.78; H, 3.97; N, 14.58.

*4.4.27. 5-(2-Phenylhydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′a**).* Brownish yellow powder, yield: 93% (46 mg; 0.2 mmol scale), mp 298−299 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.24 (br s, 1H, −N*H*), 12.61 (br s, 1H, −N*H*), 12.45 (br s, 1H, −N*H*), 7.62 (d, 2H, J = 7.6 Hz, Ar-H), 7.49−7.46 (m, 2H, Ar-H), 7.29−7.26 (m, 1H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.59 (−NHCSNH−), 160.07 (−NHCO−), 158.41 (−NHCO−), 141.25 (*C*), 129.84 (2× *C*H), 126.63 (*C*H), 118.76 (*C*), 117.09 (2× *C*H) ppm. HRMS (TOF MS ES$^+$): m/z 271.0260 [M + Na]$^+$ calcd for $C_{10}H_8N_4O_2SNa$; found, 271.0264.

*4.4.28. 2-Thioxo-5-(2-(o-tolyl)hydrazono)-dihydropyrimidine-4,6(1H,5H)-dione (**4′b**).* Pale brown powder, yield: 95% (50 mg; 0.2 mmol scale), mp 285−286 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.60 (br s, 1H, −N*H*), 12.68 (br s, 1H, −N*H*), 12.49 (br s, 1H, −N*H*), 7.68 (d, 1H, J = 8.4 Hz, Ar-H), 7.38−7.32 (m, 2H, Ar-H), 7.19 (t, 1H, J = 7.2 Hz, Ar-H), 2.37 (s, 3H, Ar-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.47 (−NHCSNH−), 160.77 (−NHCO−), 158.29 (−NHCO−), 139.03 (*C*), 131.30 (*C*H), 127.75 (*C*H), 126.48 (*C*H), 126.18 (*C*), 119.47 (*C*), 115.02 (*C*H), 16.36 (Ar-*C*H_3) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.24; H, 3.89; N, 21.48.

*4.4.29. 2-Thioxo-5-(2-(p-tolyl)hydrazono)-dihydropyrimidine-4,6(1H,5H)-dione (**4′c**).* Orange powder, yield: 94% (49 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.29 (br s, 1H, −N*H*), 12.57 (br s, 1H, −N*H*), 12.40 (br s, 1H, −N*H*), 7.51 (d, 2H, J = 8.4 Hz, Ar-H), 7.28 (d, 2H, J = 8.4 Hz, Ar-H), 2.32 (s, 3H, Ar-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.43 (−NHCSNH−), 160.06 (−NHCO−), 158.36 (−NHCO−), 138.92 (*C*), 136.34 (*C*), 130.22 (2× *C*H), 118.18 (*C*), 117.05 (2× *C*H), 20.64 (Ar-*C*H_3) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.22; H, 3.79; N, 21.27.

*4.4.30. 5-(2-(2-Methoxyphenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′d**).* Red powder, yield: 95% (50 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.55 (br s, 1H, −N*H*), 12.59 (br s, 1H, −N*H*), 12.43 (br s, 1H, −N*H*), 7.66 (d, 1H, J = 8.0 Hz, Ar-H), 7.28−7.25 (m, 1H, Ar-H), 7.19 (d, 1H, J = 8.0 Hz, Ar-H), 7.09 (t, 1H, J = 7.6 Hz, Ar-H), 3.95 (s, 3H, Ar-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.44 (−NHCSNH−), 160.41 (−NHCO−), 158.32 (−NHCO−), 148.45 (*C*), 129.66 (*C*), 127.39 (*C*H), 121.78 (*C*H), 119.43

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(*C*), 115.13 (*C*H), 112.27 (*C*H), 56.38 (Ar-O*C*H$_3$) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.62; N, 20.13. Found: C, 47.45; H, 3.66; N, 20.17.

*4.4.31. 5-(2-(4-Methoxyphenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′e**).* Red powder, yield: 77% (43 mg; 0.2 mmol scale), mp 280−282 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.41 (s, 1H, −N*H*), 12.52 (s, 1H, −N*H*), 12.36 (s, 1H, −N*H*), 7.59 (d, 2H, J = 8.8 Hz, Ar-H), 7.05 (d, 2H, J = 8.8 Hz, Ar-H), 3.79 (s, 3H, Ar-OC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.29 (−NHCSNH−), 160.07 (−NHCO−), 158.42 (−NHCO−), 158.29 (*C*), 134.64 (*C*), 118.76 (2× *C*H), 117.59 (*C*), 115.03 (2× *C*H), 55.52 (Ar-O*C*H$_3$) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.62; N, 20.13. Found: C, 47.33; H, 3.69; N, 20.27.

*4.4.32. 5-(2-(4-(Methylthio)phenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′f**).* Brownish red powder, yield: 85% (50 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.28 (br s, 1H, −N*H*), 12.57 (br s, 1H, −N*H*), 12.41 (br s, 1H, −N*H*), 7.58 (d, 2H, J = 8.8 Hz, Ar-H), 7.35 (d, 2H, J = 8.8 Hz, Ar-H), 3.35 (s, 3H, Ar-SC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.39 (−NHCSNH−), 159.97 (−NHCO−), 158.30 (−NHCO−), 138.46 (*C*), 136.77 (*C*), 126.93 (2× *C*H), 118.33 (*C*), 117.72 (2× *C*H), 14.78 (Ar-SC*H*$_3$) ppm. Elemental Anal. Calcd (%) for $C_{11}H_{10}N_4O_2S_2$: C, 44.88; H, 3.42; N, 19.03. Found: C, 44.69; H, 3.37; N, 19.17.

*4.4.33. 2-Thioxo-5-(2-(4-(trifluoromethoxy)phenyl)hydrazono)dihydropyrimidine-4,6(1H,5H)-dione (**4′g**).* Yellow powder, yield: 77% (51 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (br s, 2H, 2× −N*H*), 7.73 (d, 2H, J = 8.8 Hz, Ar-H), 7.48 (d, 2H, J = 8.8 Hz, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.73 (−NHCSNH−), 159.17 (−NHCO−), 146.16 (−NHCO−), 140.58 (*C*), 122.63 (2× *C*H), 121.49 (*C*), 119.36 (*C*), 118.94 (*C*), 118.83 (2× *C*H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ −56.99 ppm. Elemental Anal. Calcd (%) for $C_{11}H_7F_3N_4O_3S$: C, 39.76; H, 2.12; N, 16.86. Found: C, 39.61; H, 2.17; N, 16.92.

*4.4.34. 5-(2-(2-Nitrophenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′h**).* Orange yellow powder, yield: 75% (44 mg; 0.2 mmol scale), mp 277−279 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 15.24 (s, 1H, −N*H*), 12.77 (s, 1H, −N*H*), 12.61 (s, 1H, −N*H*), 8.28 (d, 1H, J = 8.0 Hz, Ar-H), 8.09 (d, 1H, J = 8.4 Hz, Ar-H), 7.92−7.88 (m, 1H, Ar-H), 7.43−7.39 (m, 1H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.89 (−NHCSNH−), 159.40 (−NHCO−), 157.97 (−NHCO−), 137.32 (*C*), 136.68 (*C*H), 135.72 (*C*), 126.14 (*C*H), 125.20 (*C*H), 122.80 (*C*), 117.39 (*C*H) ppm. Elemental Anal. Calcd (%) for $C_{10}H_7N_5O_4S$: C, 40.96; H, 2.41; N, 23.88. Found: C, 40.78; H, 2.36; N, 23.75.

*4.4.35. 5-(2-(4-Bromophenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′i**).* Yellow powder, yield: 78% (51 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.10 (br s, 1H, −N*H*), 12.60 (br s, 1H, −N*H*), 12.45 (br s, 1H, −N*H*), 7.65 (d, 2H, J = 8.8 Hz, Ar-H), 7.59 (d, 2H, J = 8.8 Hz, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.59 (−NHCSNH−), 159.76 (−NHCO−), 158.25 (−NHCO−), 140.73 (*C*), 132.53 (2× *C*H), 119.20 (*C*), 118.98 (2× *C*H), 118.48 (*C*) ppm. Elemental Anal. Calcd (%) for $C_{10}H_7BrN_4O_2S$: C, 36.71; H, 2.16; N, 17.13. Found: C, 36.59; H, 2.21; N, 17.24.

*4.4.36. 5-(2-(4-(4-Chlorophenoxy)phenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′j**).* Deep orange powder, yield: 92% (69 mg; 0.2 mmol scale), mp >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.30 (br s, 1H, −N*H*), 12.58 (br s, 1H, −N*H*), 12.42 (br s, 1H, −N*H*), 7.66−7.45 (m, 4H, Ar-H), 7.13−7.08 (m, 4H, Ar-H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 177.49 (−NHCSNH−), 159.97 (−NHCO−), 158.42 (−NHCO−), 155.44 (*C*), 154.82 (*C*), 137.32 (*C*), 130.07 (2× *C*H), 127.58 (*C*), 120.48 (2× *C*H), 119.96 (2× *C*H), 119.05 (2× *C*H), 118.44 (*C*) ppm. Elemental Anal. Calcd (%) for $C_{16}H_{11}ClN_4O_3S$: C, 51.27; H, 2.96; N, 14.95. Found: C, 51.14; H, 2.91; N, 14.82.

*4.4.37. 1,3-Diethyl-5-(2-phenylhydrazineylidene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′k**).* Brownish yellow powder, yield: 85% (52 mg; 0.2 mmol scale), mp 192−193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.88 (br s, 1H, −N*H*), 7.58 (d, 2H, J = 8.0 Hz, Ar-H), 7.46−7.42 (m, 2H, Ar-H), 7.31−7.27 (m, 1H, Ar-H), 4.62−4.52 (m, 4H, 2× −NC*H*$_2$CH$_3$), 1.34−1.31 (m, 6H, 2× −NCH$_2$C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.70 (S=*C*(−NC$_2$H$_5$)$_2$), 159.45 (−N(C$_2$H$_5$)*C*O−), 157.67 (−N-(C$_2$H$_5$)*C*O−), 140.80 (2*C*), 129.92 (2× *C*H), 127.76 (*C*H), 117.69 (2× *C*H), 43.89 (−*C*H$_2$CH$_3$), 42.72 (−*C*H$_2$CH$_3$), 12.49 (−*C*H$_2$CH$_3$), 12.29 (−*C*H$_2$CH$_3$) ppm. HRMS (TOF MS ES$^+$): m/z 305.1067 [M + H]$^+$ calcd for $C_{14}H_{16}N_4O_2SH$; found, 305.1068; m/z 327.0886 [M + Na]$^+$ calcd for $C_{14}H_{16}N_4O_2SNa$; found, 327.0888.

*4.4.38. 1,3-Diethyl-2-thioxo-5-(2-(o-tolyl)hydrazineylidene)dihydropyrimidine-4,6(1H,5H)-dione (**4′l**).* Yellow powder, yield: 94% (60 mg; 0.2 mmol scale), mp 175−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.09 (br s, 1H, −N*H*), 7.97 (d, 1H, J = 8.0 Hz, Ar-H), 7.34−7.30 (m, 1H, Ar-H), 7.24−7.18 (m, 2H, Ar-H), 4.62−4.54 (m, 4H, 2× −NC*H*$_2$CH$_3$), 2.48 (s, 3H, Ar-C*H*$_3$), 1.35−1.31 (m, 6H, 2× −NCH$_2$C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.69 (S=*C*(−NC$_2$H$_5$)$_2$), 159.60 (−N(C$_2$H$_5$)*C*O−), 157.82 (−N(C$_2$H$_5$)*C*O−), 139.15 (*C*), 131.24 (*C*H), 127.99 (*C*H), 127.59 (*C*H), 126.82 (*C*), 118.30 (*C*), 116.83 (*C*H), 43.91 (−*C*H$_2$CH$_3$), 42.74 (−*C*H$_2$CH$_3$), 17.13 (Ar-*C*H$_3$), 12.54 (−*C*H$_2$CH$_3$), 12.30 (−*C*H$_2$CH$_3$) ppm. Elemental Anal. Calcd (%) for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 56.71; H, 5.77; N, 17.53.

*4.4.39. 1,3-Diethyl-2-thioxo-5-(2-(p-tolyl)hydrazono)-dihydropyrimidine-4,6(1H,5H)-dione (**4′m**).* Orange yellow powder, yield: 87% (52 mg; 0.2 mmol scale), mp 224−225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.94 (br s, 1H, −N*H*), 7.47 (d, 2H, J = 8.0 Hz, Ar-H), 7.23 (d, 2H, J = 8.4 Hz, Ar-H), 4.60−4.51 (m, 4H, 2× −NC*H*$_2$CH$_3$), 2.36 (s, 3H, Ar-C*H*$_3$), 1.33−1.29 (m, 6H, 2× −NCH$_2$C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.66 (S=*C*(−NC$_2$H$_5$)$_2$), 159.47 (−N(C$_2$H$_5$)*C*O−), 157.75 (−N(C$_2$H$_5$)*C*O−), 138.52 (*C*), 138.21 (*C*), 130.49 (2× *C*H), 117.65 (2× *C*H), 117.27 (*C*), 43.83 (−*C*H$_2$CH$_3$), 42.65 (−*C*H$_2$CH$_3$), 21.29 (Ar-*C*H$_3$), 12.48 (−*C*H$_2$CH$_3$), 12.27 (−*C*H$_2$CH$_3$) ppm. Elemental Anal. Calcd (%) for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 56.69; H, 5.74; N, 17.69.

*4.4.40. 1,3-Diethyl-5-(2-(2-methoxyphenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′n**).* Orange yellow powder, yield: 91% (61 mg; 0.2 mmol scale), mp 248−249 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.97 (br s, 1H, −N*H*), 7.97 (dd, 1H, J = 8.0 and 0.8 Hz, Ar-H), 7.27−7.23 (m, 1H, Ar-H), 7.08−7.04 (m, 1H, Ar-H), 6.98 (d, 1H, J = 8.4 Hz, Ar-H), 4.63−4.55 (m, 4H, 2× −NC*H*$_2$CH$_3$), 4.01 (s, 3H,

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Ar-OCH_3), 1.35−1.31 (m, 6H, 2× −NCH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.79 (S=C(−NC$_2$H$_5$)$_2$), 159.13 (−N(C$_2$H$_5$)CO−), 158.01 (−N-(C$_2$H$_5$)CO-), 149.40 (C), 130.10 (C), 128.31 (CH), 121.98 (CH), 118.13 (C), 117.16 (CH), 111.33 (CH), 56.29 (Ar-OCH_3), 43.88 (−NCH_2CH$_3$), 42.68 (−NCH_2CH$_3$), 12.57 (−NCH$_2$$CH_3$), 12.33 (−NCH$_2$$CH_3$) ppm. Elemental Anal. Calcd (%) for $C_{15}H_{18}N_4O_3S$: C, 53.88; H, 5.43; N, 16.75. Found: C, 53.75; H, 5.49; N, 16.87.

*4.4.41. 1,3-Diethyl-5-(2-(4-methoxyphenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′o**).* Red powder, yield: 88% (59 mg; 0.2 mmol scale), mp 205−206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.08 (br s, 1H, −NH), 7.54 (d, 2H, J = 8.8 Hz, Ar-H), 6.95 (d, 2H, J = 8.8 Hz, Ar-H), 4.61−4.51 (m, 4H, 2× −NCH_2CH$_3$), 3.83 (s, 3H, Ar-OCH_3), 1.33−1.29 (m, 6H, 2× −NCH$_2$$CH_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.61 (S=C(−NC$_2$H$_5$)$_2$), 159.58 (−N-(C$_2$H$_5$)CO−), 159.56 (C), 157.86 (−N(C$_2$H$_5$)CO−), 134.34 (C), 119.26 (2× CH), 116.94 (C), 115.20 (2× CH), 55.76 (Ar-OCH_3), 43.79 (−NCH_2CH$_3$), 42.62 (−NCH_2CH$_3$), 12.48 (−NCH$_2$$CH_3$), 12.27 (−NCH$_2$$CH_3$) ppm. Elemental Anal. Calcd (%) for $C_{15}H_{18}N_4O_3S$: C, 53.88; H, 5.43; N, 16.75. Found: C, 53.74; H, 5.50; N, 16.66.

*4.4.42. 1,3-Diethyl-5-(2-(4-(methylthio)phenyl)-hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′p**).* Red powder, yield: 81% (57 mg; 0.2 mmol scale), mp 185−187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.97 (br s, 1H, −NH), 7.51 (d, 2H, J = 8.8 Hz, Ar-H), 7.28 (d, 2H, J = 8.4 Hz, Ar-H), 4.59−4.53 (m, 4H, 2× −NCH_2CH$_3$), 2.51 (s, 3H, Ar-SCH_3), 1.33−1.29 (m, 6H, 2× −NCH$_2$$CH_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.58 (S=C(−NC$_2$H$_5$)$_2$), 159.51 (−N(C$_2$H$_5$)CO−), 157.72 (−N(C$_2$H$_5$)CO−), 139.07 (C), 138.05 (C), 127.38 (2× CH), 118.14 (2× CH), 117.47 (C), 43.89 (−NCH_2CH$_3$), 42.72 (−NCH_2CH$_3$), 15.82 (Ar-SCH_3), 12.50 (−NCH$_2$$CH_3$), 12.29 (−NCH$_2$$CH_3$) ppm. Elemental Anal. Calcd (%) for $C_{15}H_{18}N_4O_2S_2$: C, 51.41; H, 5.18; N, 15.99. Found: C, 51.56; H, 5.13; N, 15.87.

*4.4.43. 1,3-Diethyl-2-thioxo-5-(2-(4-((trifluoromethyl)-thio)phenyl)hydrazono)dihydropyrimidine-4,6(1H,5H)-dione (**4′q**).* Bright yellow powder, yield: 83% (67 mg; 0.2 mmol scale), mp 231−232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.78 (br s, 1H, −NH), 7.72 (d, 2H, J = 8.4 Hz, Ar-H), 7.62 (d, 2H, J = 8.8 Hz, Ar-H), 4.61−4.52 (m, 4H, 2× −NCH_2CH$_3$), 1.34−1.30 (m, 6H, 2× −NCH$_2$$CH_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.52 (S=C(−NC$_2$H$_5$)$_2$), 159.34 (−N-(C$_2$H$_5$)CO−), 157.31 (−N(C$_2$H$_5$)CO−), 142.88 (C), 138.06 (2× CH), 129.44 (−SCF_3, J_{CF} = 306 Hz), 122.71 (C), 118.76 (C), 118.20 (2× CH), 44.04 (−NCH_2CH$_3$), 42.90 (−NCH_2CH$_3$), 12.48 (−NCH$_2$$CH_3$), 12.27 (−NCH$_2$$CH_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −42.79 ppm. Elemental Anal. Calcd (%) for: $C_{15}H_{15}F_3N_4O_2S_2$: C, 44.55; H, 3.74; N, 13.85. Found: C, 44.69; H, 3.69; N, 13.77.

*4.4.44. 1,3-Diethyl-2-thioxo-5-(2-(4-(trifluoromethoxy)-phenyl)hydrazono)dihydropyrimidine-4,6(1H,5H)-dione (**4′r**).* Yellow powder, yield: 85% (65 mg; 0.2 mmol scale), mp 176−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.86 (br s, 1H, −NH), 7.61 (d, 2H, J = 8.8 Hz, Ar-H), 7.30 (d, 2H, J = 8.8 Hz, Ar-H), 4.62−4.53 (m, 4H, 2× −NCH_2CH$_3$), 1.34−1.31 (m, 6H, 2× −NCH$_2$$CH_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.61 (S=C(−NC$_2$H$_5$)$_2$), 159.45 (−N(C$_2$H$_5$)CO−), 157.50 (−N(C$_2$H$_5$)CO−), 147.97 (C), 139.33 (C), 122.60 (2× CH), 118.79 (2× CH), 118.40 (C), 118.23 (C), 43.98 (−NCH_2CH$_3$), 42.83 (−NCH_2CH$_3$), 12.49 (−NCH$_2$$CH_3$), 12.28 (−NCH$_2$$CH_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.01 ppm. Elemental Anal. Calcd (%) for $C_{15}H_{15}F_3N_4O_3S$: C, 46.39; H, 3.89; N, 14.43. Found: C, 46.51; H, 3.93; N, 14.51.

*4.4.45. 1,3-Diethyl-5-(2-(2-nitrophenyl)hydrazono)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′s**).* Yellow powder, yield: 78% (59 mg; 0.2 mmol scale), mp 155−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.79 (br s, 1H, −NH), 8.35 (d, 1H, J = 8.4 Hz, Ar-H), 8.29 (d, 1H, J = 8.0 Hz, Ar-H), 7.77−7.74 (m, 1H, Ar-H), 7.38−7.34 (m, 1H, Ar-H), 4.61−4.56 (m, 4H, 2× −NCH_2CH$_3$), 1.35−1.31 (m, 6H, 2× −NCH$_2$$CH_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.55 (S=C(−NC$_2$H$_5$)$_2$), 158.01 (−N(C$_2$H$_5$)CO−), 157.22 (−N(C$_2$H$_5$)CO−), 137.36 (C), 136.46 (C), 136.23 (CH), 126.13 (CH), 125.95 (CH), 120.96 (C), 118.92 (CH), 44.11 (−NCH_2CH$_3$), 43.11 (−NCH_2CH$_3$), 12.53 (−NCH$_2$$CH_3$), 12.31 (−NCH$_2$$CH_3$) ppm. Elemental Anal. Calcd (%) for $C_{14}H_{15}N_5O_4S$: C, 48.13; H, 4.33; N, 20.05. Found: C, 48.02; H, 4.38; N, 20.14.

*4.4.46. 5-(2-(4-Bromophenyl)hydrazono)-1,3-diethyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′t**).* Brownish yellow powder, yield: 72% (55 mg; 0.2 mmol scale), mp 255−257 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.79 (br s, 1H, −NH), 7.54 (d, 2H, J = 8.8 Hz, Ar-H), 7.44 (d, 2H, J = 8.8 Hz, Ar-H), 4.59−4.49 (m, 4H, 2× −NCH_2CH$_3$), 1.32−1.29 (m, 6H, 2× −NCH$_2$$CH_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.56 (S=C(−NC$_2$H$_5$)$_2$), 159.42 (−N(C$_2$H$_5$)CO−), 157.49 (−N(C$_2$H$_5$)CO−), 139.88 (C), 133.02 (2× CH), 120.92 (C), 118.99 (2× CH), 118.09 (C), 43.95 (−NCH_2CH$_3$), 42.80 (−NCH_2CH$_3$), 12.49 (−NCH$_2$$CH_3$), 12.28 (−NCH$_2$$CH_3$) ppm. Elemental Anal. Calcd (%) for: $C_{14}H_{15}BrN_4O_2S$: C, 43.87; H, 3.94; N, 14.62. Found: C, 43.73; H, 3.99; N, 14.69.

*4.4.47. 5-(2-(2,5-Dichlorophenyl)hydrazono)-1,3-diethyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (**4′u**).* Yellow powder, yield: 86% (64 mg; 0.2 mmol scale), mp 264−266 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.91 (br s, 1H, −NH), 8.04 (d, 1H, J = 2.0 Hz, Ar-H), 7.36 (d, 1H, J = 8.4 Hz, Ar-H), 7.17 (dd, 1H, J = 8.8 and 2.4 Hz, Ar-H), 4.62−4.54 (m, 4H, 2× −NCH_2CH$_3$), 1.35−1.31 (m, 6H, 2× −NCH$_2$$CH_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.54 (S=C(−NC$_2$H$_5$)$_2$), 159.08 (−N(C$_2$H$_5$)CO−), 157.24 (−N-(C$_2$H$_5$)CO−), 138.56 (C), 134.91 (C), 130.85 (CH), 127.47 (CH), 121.09 (C), 119.74 (C), 117.91 (CH), 44.09 (−NCH_2CH$_3$), 42.99 (−NCH_2CH$_3$), 12.53 (−NCH$_2$$CH_3$), 12.29 (−NCH$_2$$CH_3$) ppm. Elemental Anal. Calcd (%) for: $C_{14}H_{14}Cl_2N_4O_2S$: C, 45.05; H, 3.78; N, 15.01. Found: C, 45.17; H, 3.82; N, 15.12.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03073.

Scanned copies of respective ^{1}H NMR, ^{13}C NMR, and DEPT-135 spectra for all the synthesized compounds **4a−4z** and **4′a−4′u**; ^{19}F NMR (for fluorine atom-containing molecules such as **4g**, **4h**, **4n**, **4v**, **4′g**, **4′q**, and **4′r**), 2D NMR (for one representative compound, **4t**), and HRMS (for representative compounds **4a**, **4p**, **4′a**, and **4′k**) spectra, and X-ray single crystallographic analysis for a representative entry, 5-(2-(2-

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methoxyphenyl)hydrazono)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**4d**) (PDF)

CCDC 2170064 contains the supplementary crystallographic data for **4d** that can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif. Single X-ray crystallographic data for **4d** (CIF)

NMR FID FAIR data, including the primary NMR FID files, for compounds **4a**−**4z** and **4′a**−**4′u** (ZIP)

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Notes

The authors declare no competing financial interest.

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