

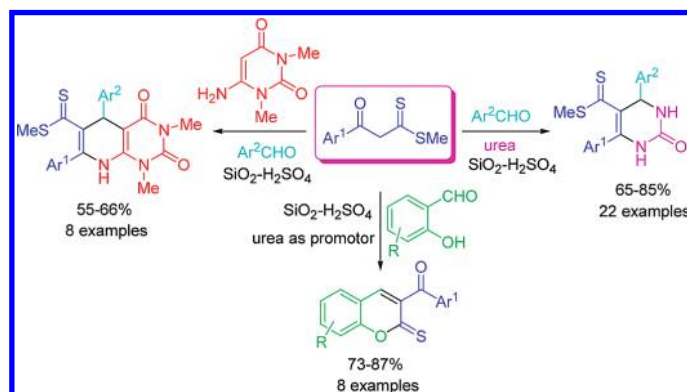
Biginelli and Hantzsch-Type Reactions Leading to Highly Functionalized Dihydropyrimidinone, Thiocoumarin, and Pyridopyrimidinone Frameworks via Ring Annulation with β -Oxodithioesters

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Received August 13, 2010



An efficient and highly convergent route to dihydropyrimidinones (DHPMs) and hitherto unreported dihydropyridopyrimidinones has been developed by one-pot, three-component cyclocondensation of aromatic aldehydes, β -oxodithioesters, and urea/6-amino-1,3-dimethyluracil in the presence of recyclable $\text{SiO}_2\text{--H}_2\text{SO}_4$. On the other hand, salicylaldehyde, β -oxodithioester, and urea reacted under similar conditions to afford the 3-aryl/heteroaryl-2*H*-chromen-2-thiones in high yields instead of Biginelli product. The attractive feature of this approach is the synthesis of three important bioactive heterocyclic frameworks from the same β -oxodithioester under the similar reaction conditions, making this new strategy highly useful in diversity-oriented synthesis (DOS).

Introduction

The Biginelli dihydropyrimidinone MCR has come a long way since its discovery 117 years ago in 1893 by Italian chemist Pietro Biginelli.¹ From the preparation of simple pyrimidine heterocycles in the late 19th century to the generation of targeted compound libraries of biofunctional dihydropyrimidinones (DHPMs) and the enantioselective

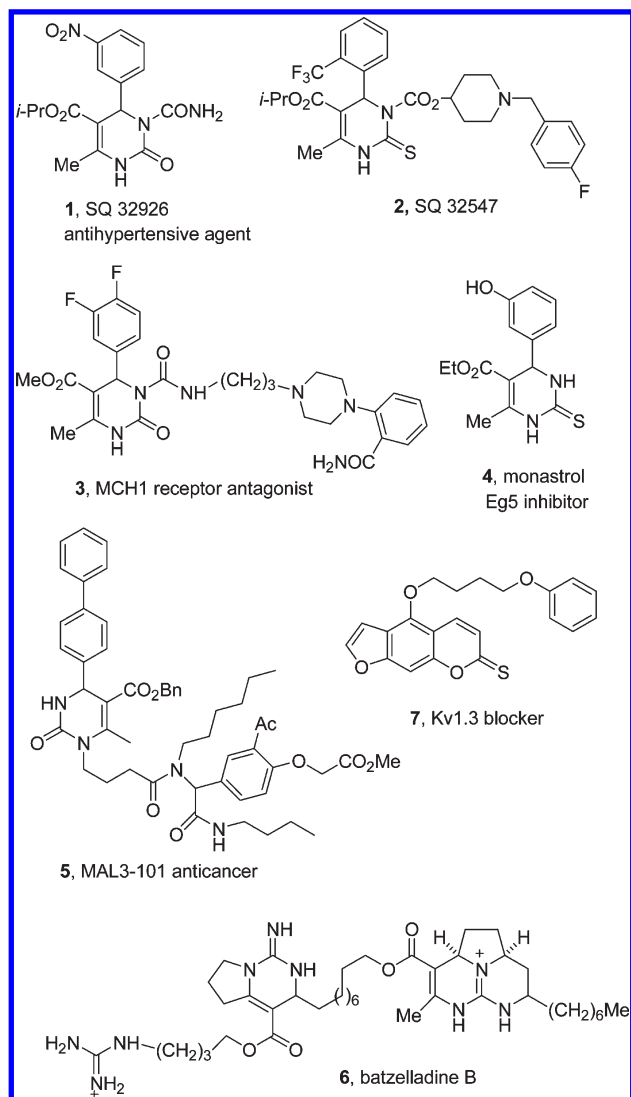
total synthesis of complex natural products, the Biginelli MCR^{2,3} has been adapted successfully to the needs and expectations of modern synthetic organic chemistry. The interesting and multifaceted biological profiles of dihydropyrimidinones^{4,5} have been explored through the generation of libraries of compounds. In the past decades, a broad range of biological effects⁶ including antiviral, antitumor, antibacterial, analgesic, and anti-inflammatory activities have been ascribed to Biginelli compounds. Moreover, appropriately functionalized DHPMs (Chart 1) exhibit

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CHART 1. Examples of Biologically Active Heterocyclic Frameworks

a variety of pharmacological activities such as antihypertensive agents (**1**, **2**),^{4c,7} α_1 adrenoceptor-selective antagonist (**3**),^{5c,8}

mitotic kinesin Eg5 inhibitor (monastrol, **4**), and anticancer (**5**, MAL3–101).⁹ Furthermore, apart from synthetic DHPM derivatives, several marine natural products containing DHPM skeleton such as batzelladine B (**6**), ptilomycalines, and crambescidines with interesting biological activities^{4d,5e,f} have recently been isolated. Similarly, thiocoumarins display a remarkable array of biochemical and pharmacological actions¹⁰ such as **7** is used as blocker^{10e} of the lymphocyte potassium channel Kv1.3. Another heterocyclic core unit dihydropyridopyrimidinones, which is structurally similar with the DHPM also display the promising pharmacological activity such as adenosine kinase inhibitor,^{11a} Abl kinase inhibitor,^{11b} tyrosine phosphatase inhibitor,^{11c} antiviral,^{11d} in treatment of diarrhea,^{11e} and as a Ca^{2+} channel modulator. The diverse range of biological activities of these moieties has stimulated considerable interest to synthesize these units via a new and efficient route.

In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction shown in Scheme 1 was gradually extended by variation of all the three building blocks allowing access to a large number of attractive multifunctionalized DHPMs. A plethora of useful methodologies involving various types of homogeneous and heterogeneous catalysts^{12,13} have been elaborated in order to keep the simplicity and to improve the efficiency of the classical Biginelli protocol and to simultaneously overcome

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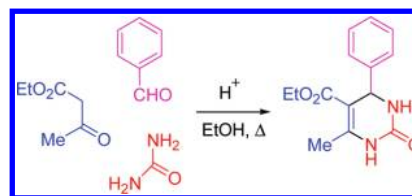
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its undesirable features. Asymmetric¹⁴ and chemo/regioselective synthesis¹⁵ of Biginelli products using organocatalysts have been developed. Ammonium chloride,^{16a} ammonium and tetrabutylammonium bromides,^{16b,c} copper nitrate,¹⁷ SiO₂-HClO₄,^{18a} CaF₂,^{18b} Al₂O₃-MeSO₃H,^{18c} polymer-supported aminoformoyl diphenylammonium triflate,^{18d} metal triflate/triflimide,¹⁹ piperidinium triflate,^{19k} sodium chloride,^{20a} thiamine hydrochloride,^{20b} chlorotrimethylsilane,^{20c} aluminum-planted mesoporous silica,^{21a} graphite supported lanthanum chloride,^{21b} hexaquaaluminum(III) tetrafluoroborate^{21c} and pyrazolidine dihydrochloride²² have also been utilized as efficient catalysts for the Biginelli reaction. Recently, a base-catalyzed²³ and modified syntheses of DHPMs in aqueous media have also been carried out.^{20b,24} The use of the common open-chain β -dicarbonyl compounds in Biginelli reactions has been extended

SCHEME 1. Biginelli Dihydropyrimidinone Synthesis



to the use of cyclic β -diketones,²⁵ β -ketolactones,²⁶ cyclic β -diesters²⁷ or β -diamides,^{27,28} benzocyclic ketones,²⁹ α -keto acids,²⁹ diketenes,³⁰ and 3-amino-1,2,4-triazole as urea component.³¹

Despite the plethora of different catalysts ranging over diverse methods published so far also suffer from drawbacks, such as limitation of applicable β -ketoesters, the need for strong acids, toxic organic solvents and catalysts, cumbersome experimental procedures, and lacking generality. Therefore, more general, efficient and viable routes employing recyclable catalysts in Biginelli synthesis are very much desirable in view of their broad array of biological activity and would be of great relevance to both synthetic and medicinal chemists. The use of solid supported catalysts has become highly desirable in recent years to meet the environmental considerations.³² It is well-known that silica-sulfuric acid is a cheap, nontoxic, and stable acidic reagent,³³ which has been extensively utilized in various synthetic transformations³⁴ due to its several advantages such as operational simplicity, reusability, low price, and air tolerance. In continuation of our recent work³⁵ on the synthesis of heterocycles by the development of new methodology, in this paper, we report for the first time silica-sulfuric acid

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TABLE 1. Synthesis of β -Oxodithioesters **9**

entry	Ar ¹	dithioester	yield ^a (%)
1	C ₆ H ₅	9a	72
2	4-Cl·C ₆ H ₄	9b	75
3	4-MeO·C ₆ H ₄	9c	73
4	2-thienyl	9d	80
5	2-furyl	9e	70

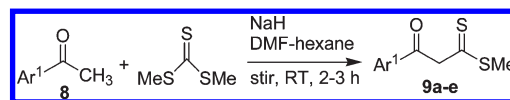
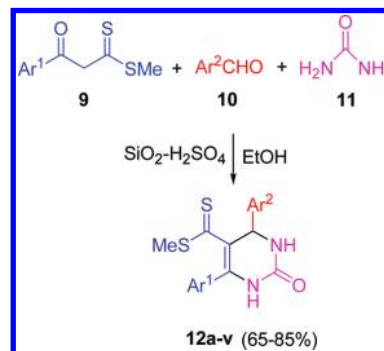
^aIsolated yields.

promoted Biginelli- and Hantzsch-type reactions that allowed the formation of a diverse range of new heterocyclic frameworks via ring annulation of β -oxodithioesters by aldehydes. A continuing exciting future for the Biginelli and Hantzsch-type reactions in the 21st century is therefore secured.

Results and Discussion

Our literature survey at this stage revealed that Singh and Devi^{12h} utilized β -oxodithioesters for the first time as a β -dicarbonyl component in Biginelli reaction catalyzed by SnCl₂, which is applicable for only limited aldehydes and β -oxodithioesters. Moreover, the catalyst used cannot be recycled and the temperature is also high (100 °C). Furthermore, there was no report of synthesis of DHPMs from **9**, thus warranting a more elaborate investigation. We therefore became interested in devising more general synthetic strategy utilizing 3-aryl/heteroaryl- β -oxodithioesters **9** as the versatile templates for the construction of DHPMs **12** (Scheme 3) and other bioactive heterocyclic frameworks **14** and **17** in the presence of recyclable SiO₂–H₂SO₄ (Schemes 5 and 7). Access to a diverse collection of starting materials is critical to render any method as practical. While many β -dicarbonyl compounds are commercially available, the same cannot be said for β -oxodithioesters. The desired β -oxodithioesters³⁶ **9a–e** (Table 1) were synthesized in good yields (70–80%) by stirring ketones **8** with (S,S)-dimethyl trithiocarbonate in the presence of NaH in DMF–hexane (1:4) mixture at room temperature (Scheme 2). The synthesis of DHPMs **12** (Scheme 3) was first undertaken. Thus, in a typical general procedure, 4-nitrobenzaldehyde **10a** (1.1 mmol), urea **11** (1.2 mmol), and 3-oxo-3-(2-furyl)dithiopropionic acid methyl ester **9e** (1.0 mmol) were mixed in minimum amount of dry ethanol to get a paste like mixture. SiO₂–H₂SO₄ was added to pasty mixture and was heated at 80 °C to afford DHPM **12u** in 85% yield (Table 3, entry 21). The new methodology allows facile introduction of substituents at 4-, 5-, and 6-positions of the DHPM skeleton and flexibility for the construction of novel pyridopyrimidinone and thiocoumarin ring systems.

Initially, a variety of alternate catalysts such as *p*-TSA, oxalic acid, camphorsulfonic acid, L-proline, cyanuric chloride, BF₃·OEt₂, HClO₄–SiO₂, PPA–SiO₂, HCl, HCl–SiO₂, and H₂SO₄–SiO₂ were screened to identify a suitable activator for this transformation, but only H₂SO₄–SiO₂

SCHEME 2. Synthesis of β -Oxodithioesters **9**SCHEME 3. Synthesis of 5-Methylmercaptothiocabonyl-4,6-diaryl-1,2,3,4-tetrahydropyrimidin-5-ones **12a–v**TABLE 2. Optimization of the Catalyst on Model Reaction^a

entry	catalyst	time ^b (h)	yield ^c (%)
1	<i>p</i> -TSA	4	51
2	oxalic acid	5	53
3	camphorsulfonic acid	5	40
4	L-proline	5	35
5	cyanuric chloride	4	15
6	HClO ₄ –SiO ₂	4	55
7	PPA–SiO ₂	4	60
8	BF ₃ ·OEt ₂	3.5	80
9	H ₂ SO ₄ –SiO ₂	2.5	85
10	HCl	3.5	70
11	HCl–SiO ₂	5	50

^aReaction of 4-nitrobenzaldehyde (1.1 mmol), 3-oxo-3-(2-furyl)dithiopropionic acid methyl ester (1.0 mmol), and urea (1.2 mmol).
^bTime required. ^cIsolated yields.

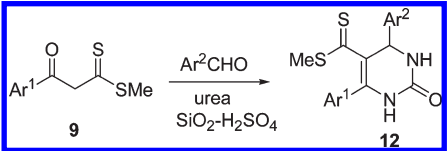
and BF₃·OEt₂ facilitated DHPMs formation in good yields (Table 2). H₂SO₄–SiO₂ is a versatile stable acidic reagent uniquely suited for this one-pot transformation, acting as both a Lewis acid and a mild dehydrating reagent. The relatively mild nature of this reagent achieved a high degree of functional group tolerance. Even extremely electron-rich aromatic β -oxodithioesters such as **9d** and **9e** (Table 1) proceeded smoothly. SiO₂–H₂SO₄ was easily recycled and used over three times without loss of activity, when 4-nitrobenzaldehyde **10a**, 3-oxo-3-phenyldithiopropionic acid methyl ester **9a**, and urea were condensed in Biginelli reaction to give **12a** (Table 3, entry 1). This feature provides a significant benefit (environmental and cost) over traditional catalysts.

Confident that the method would tolerate structural diversity, focus then shifted to optimization. A control experiment in the absence of the catalyst provided no desired product. Moreover, we also carried out this experiment under solvent-free conditions, but the desired product was not obtained. We then carried out the reaction in different solvents. The observations revealed that in aprotic solvents such as THF, DMF, and acetonitrile the product yield was found to be low, but in the case of protic solvents such as EtOH and MeOH the reaction rate as well as the product yield were found to be improved comparatively. After screening for different solvents, EtOH was found to be the

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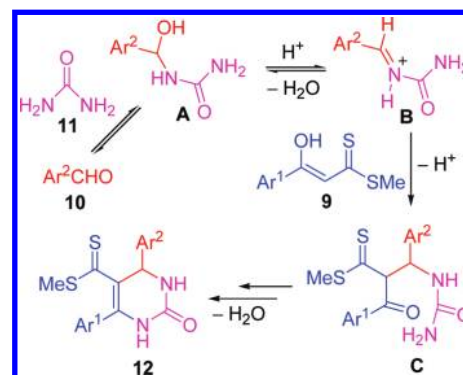
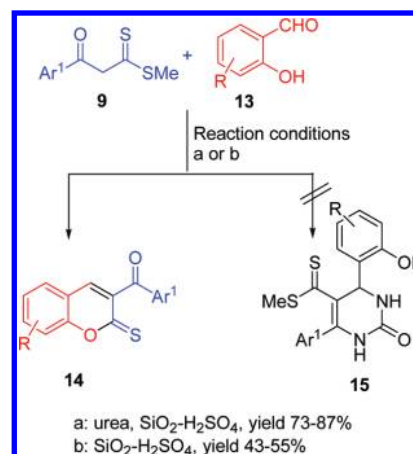
TABLE 3. Scope Exploration: Variation of Ar¹ and Ar²

					
entry	Ar ¹	Ar ²	product	time (h)	yield ^a (%)
1	C ₆ H ₅	4-NO ₂ ·C ₆ H ₄	12a	3	76
2	C ₆ H ₅	4-Br·C ₆ H ₄	12b	3	72
3	C ₆ H ₅	C ₆ H ₅	12c	3	70
4	C ₆ H ₅	4-MeO·C ₆ H ₄	12d	3.5	68
5	C ₆ H ₅	4-Cl·C ₆ H ₄	12e	3	73
6	C ₆ H ₅	2-thienyl	12f	3	65
7	4-MeO·C ₆ H ₄	4-Br·C ₆ H ₄	12g	3	78
8	4-MeO·C ₆ H ₄	4-MeO·C ₆ H ₄	12h	3	73
9	4-MeO·C ₆ H ₄	2-Cl·C ₆ H ₄	12i	3.5	69
10	4-MeO·C ₆ H ₄	C ₆ H ₅	12j	3	76
11	4-MeO·C ₆ H ₄	2-thienyl	12k	3.5	67
12	4-Cl·C ₆ H ₄	3-NO ₂ ·C ₆ H ₄	12l	3	80
13	4-Cl·C ₆ H ₄	4-MeO·C ₆ H ₄	12m	3	73
14	4-Cl·C ₆ H ₄	4-Cl·C ₆ H ₄	12n	2.5	76
15	2-thienyl	4-Cl·C ₆ H ₄	12o	3	77
16	2-thienyl	4-Br·C ₆ H ₄	12p	3	75
17	2-thienyl	3-NO ₂ ·C ₆ H ₄	12q	3	76
18	2-thienyl	C ₆ H ₅	12r	3	70
19	2-thienyl	2-MeO·C ₆ H ₄	12s	3	69
20	2-furyl	3-NO ₂ ·C ₆ H ₄	12t	2.5	82
21	2-furyl	4-NO ₂ ·C ₆ H ₄	12u	2.5	85
22	2-furyl	4-Br·C ₆ H ₄	12v	2.5	80

^aIsolated yields.

medium of choice, which afforded the products not only in good yield but also with higher reaction rates. In addition, we studied the influence of temperature on the reaction time and percentage yield. Increasing the temperature above 80 °C neither improved the yield nor reduced the reaction time whereas; lowering the temperature is detrimental to the reaction resulting in lower yields. Following the optimized reaction conditions, we extended our study using various aromatic aldehydes containing electron-withdrawing or electron-releasing substituents at the *ortho*-, *meta*- or *para*-positions. Generally, the yields are moderate to high irrespective of the steric and electronic nature of the substituents. Notably, the heteroaromatic aldehydes also afforded good yields (Table 3, entries 6 and 11). However, unfortunately, when some aliphatic aldehydes such as acetaldehyde, propionaldehyde and isobutyraldehyde were utilized the desired product was observed only in trace amount, which could not be isolated. The diversity of this protocol with respect to β -oxodithioesters **9a–e** (Table 1) was also investigated, and the results are indicated in Table 3. The structures of all the newly synthesized compounds were deduced from their satisfactory elemental and spectral (IR, ¹H, ¹³C NMR, and MS) studies. Importantly, the crystallinity of DHPM **12t** allowed for structural verification by X-ray crystallography^{41a} and, thus, unambiguous regiochemical confirmation showing *S*-configuration at chiral carbon.

Although we have not established the mechanism of reaction experimentally, a possible explanation is proposed in Scheme 4, on the basis of the literature and substrate trends. The first step in the mechanism is believed to be the condensation between the aldehyde **10** and urea **11**, with some similarities to the Mannich condensation to generate **A**. The iminium intermediate **B** generated, which is the key

SCHEME 4. Plausible Mechanism for the Synthesis of DHPMs **12**SCHEME 5. Synthesis of 2*H*-Chromene-2-thiones **14**

rate-determining step, acts as an electrophile for the nucleophilic addition of the dithioester enol **9**. The ketone carbonyl of the resulting open-chain ureide adduct **C** undergoes intramolecular cyclocondensation with the urea NH₂ followed by dehydration (facilitated by SiO₂-H₂SO₄) to give the cyclized product **12**.

To further add diversity to the DHPM framework, the β -oxodithioesters **9** were next subjected to cyclocondensation with salicylaldehyde **13** in the presence of urea. To our surprise, we could not trace any corresponding Biginelli product **15**, and only the thiocoumarin derivatives **14** were obtained in 73–87% yields (Scheme 5) in contrast to the literature data.^{4b,5a,37} The structures of all the thiocoumarins **14a–h** were confirmed with the help of spectral (IR, ¹H, ¹³C NMR, and MS) and analytical data. This result suggested nonparticipation of urea in the cyclocondensation. Thus, to ascertain the role of urea, the above cyclocondensation was carried out in the absence of urea under similar reaction condition, but this tactic resulted the same thiocoumarins **14a–h** in lower yields (43–55%). Thus, a more concise approach was exploited by carrying out the reaction in presence of urea (1 equiv), which provided **14a–h** in excellent yields (Table 4). Though the role of urea in these transformations is not clear, higher yields of thiocoumarins were

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TABLE 4. Scope Exploration for the Synthesis of **14**^a

entry	Ar ¹	R	product	time ^b (h)	yield ^c (%)
1	Ph	H	14a	3.5	76
2	Ph	3-OMe	14b	2.5	85
3	4-MeO·C ₆ H ₄	5-Br	14c	3	82
4	4-MeO·C ₆ H ₄	5-NO ₂	14d	3.5	73
5	2-thienyl	3-OMe	14e	2.5	83
6	2-thienyl	5-Br	14f	3	82
7	2-furyl	3-OEt	14g	2.5	87
8	2-furyl	5-Br	14h	3	83

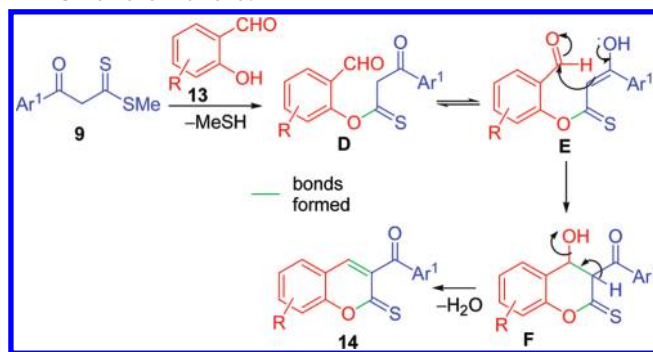
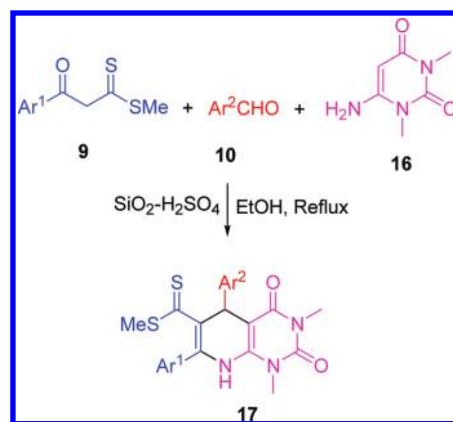
^aReaction of β -oxodithioester (1 mmol), salicylaldehyde (1 mmol), and urea (1 mmol). ^bTime required. ^cIsolated yields.

obtained in the presence of urea in analogy with the previous report.^{12h} For optimization of the reaction, 3-oxo-3-phenyl-dithiopropionic acid methyl ester **9a** (1 mmol), 2-hydroxy-3-methoxybenzaldehyde **13b** (1 mmol), and urea (1 mmol) were heated at 85 °C in the presence of H₂SO₄-SiO₂ (60 mg, 5 mmol/g) under solvent-free conditions to afford **14b** in 85% yield (Table 4, entry 2). Structural varieties of salicylaldehydes **13** and β -oxodithioesters **9** have been successfully utilized for this transformation (Table 4).

Coumarins are among the best known oxygen heterocycles and are present as a structural motif in numerous natural products including edible vegetables and fruits.³⁸ Interest in their chemistry continues unabated because they possess a broad range of biological activities³⁹ such as antiHIV,^{40a-d} anticoagulation,^{40e} antibiotic,^{40f-i} anticancer,^{40j,k} antiinflammatory,^{40l,m} antioxidant,^{40n-p} antitumor,^{40q-s} antiviral,^{40t} antihypertensive, and antimicrobial activity.

In view of the above results obtained, a plausible mechanism for the synthesis of thiocoumarin **14** is presented in Scheme 6. First, the elimination of MeSH occurs via the reaction of salicylaldehyde and β -oxodithioester to give the condensation product **D**, which undergoes enolization to its enol form **E** that participates in subsequent intramolecular aldol condensation to provide 2H-chromene-2-thiones **14** via **F**.

Many unique structures can be attained when three or more reactants were combined in a single step to afford new compounds possessing the combined features of the building blocks. Encouraged by the successful application of β -oxodithioesters **9** in the Biginelli reaction, the scope of this methodology was further expanded through the synthesis of highly functionalized dihydropyridopyrimidinones **17** using Hantzsch-type reaction (Scheme 7). These compounds

SCHEME 6. Plausible Mechanism for the Synthesis of 2H-Chromene-2-thiones **14**SCHEME 7. Synthesis of Dihydropyridopyrimidinones **17**

contain reactive functionalities for further elaboration of new molecular system, and they will likely be useful for the synthesis of biologically active molecules.

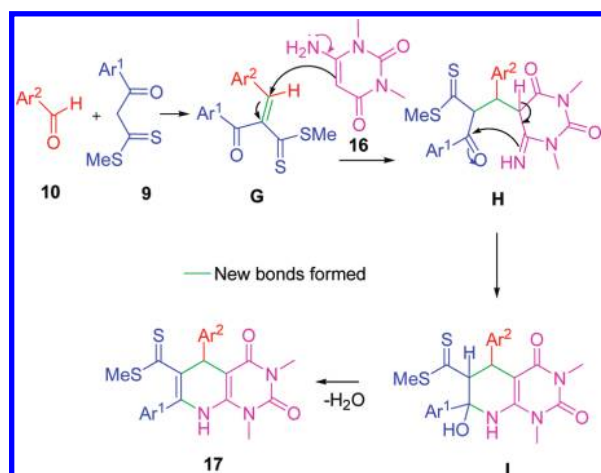
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TABLE 5. Synthesis of Dihydropyridopyrimidinones **17**

entry	Ar ¹	Ar ²	product	time (h)	yield ^a (%)
1	C ₆ H ₅	3-NO ₂ ·C ₆ H ₄	17a	6	66
2	C ₆ H ₅	3-Cl·C ₆ H ₄	17b	7	61
3	4-MeO·C ₆ H ₄	4-Br·C ₆ H ₄	17c	7	62
4	4-MeO·C ₆ H ₄	3-NO ₂ ·C ₆ H ₄	17d	6	61
5	2-thienyl	3-NO ₂ ·C ₆ H ₄	17e	6	55
6	4-Cl·C ₆ H ₄	3-NO ₂ ·C ₆ H ₄	17f	6	64
7	2-furyl	3-NO ₂ ·C ₆ H ₄	17g	6	62
8	2-furyl	4-NO ₂ ·C ₆ H ₄	17h	6	65

^aIsolated yields.**SCHEME 8.** Proposed Mechanism for the Formation of **17**

The synthesis commenced with commercially available 6-amino-1,3-dimethyluracil **16**, which upon treatment with **9** and **10** resulted in dihydropyridopyrimidinones **17** in 55–66% yields (Scheme 7). In this case, the reaction of 3-nitrobenzaldehyde, 6-amino-1,3-dimethyluracil **16**, and β -oxodithioester **9a** was taken as a model reaction and performed in the presence of SiO₂–H₂SO₄ in refluxing ethanol to afford **17a** in 66% yield (Table 5, entry 1). To check the real effect of the catalyst, the reaction was performed without catalyst, which gave the expected product **17a** in low yield (25%). To increase the yield of the desired product, catalysts such as BF₃·OEt₂ and InCl₃ were also tried that furnished the desired products but in lower yields (40–45%). Further, we carried out the above reaction under solvent-free condition also, which shows several close spots on TLC, and the desired product could not be isolated. In order to find the optimum solvent, the reaction was performed in various solvents, such as EtOH, MeOH, acetonitrile, THF, DMF, and CCl₄ at 80 °C, and it was found that EtOH provided the best result. To evaluate the scope of the reaction, various substituted aldehydes **10** and structurally varied β -oxodithioesters **9** were used, and in all cases, moderate yields were obtained (Table 5). However, when some aliphatic aldehydes such as acetaldehyde, propionaldehyde, and isobutyraldehyde were used, it led to a number of very close spots on TLC, which could not be isolated. The structures

of all the newly synthesized compounds were confirmed from their satisfactory elemental and spectral (IR, ¹H, ¹³C NMR, and MS) studies. Furthermore, the structure of **17a** has been confirmed by single-crystal X-ray data.^{41b}

A plausible mechanism is portrayed in Scheme 8. The reaction was found to proceed via aldol product **G** of aldehyde **10** and the β -oxodithioester **9**. Subsequent addition of the uracil to the aldol product followed by intramolecular cyclization and dehydration produced the dihydropyridopyrimidinone **17**. Both electron-withdrawing and electron-donating substituents on the aldehyde reactant are well tolerated in the reaction without significant impact on the yields of the products **17**.

Conclusion

In summary, β -oxodithioesters as 1,3-dicarbonyl components for the Biginelli reaction have been identified, and a diverse set of 5-methylmercaptothiocarbonyl-substituted 3,4-dihydropyrimidin-2(1*H*)-ones has been synthesized in high yields at ambient temperature. Our literature survey shows that this is the first example promoted by silica-sulfuric acid in which β -oxodithioesters as an activated β -dicarbonyl synthon is used in a Biginelli reaction. The DHPM formation is accomplished through the ability of silica-sulfuric acid to function dually as a Lewis acid and dehydrating agent in the same transformation. The methodology has been further elaborated to the corresponding 6-amino-1,3-dimethyluracil, the cyclic analogue of urea leading to pyridopyrimidinones, thus providing a further point of diversity in the newly synthesized heterocyclic framework. Further, the facile access to 3-aryl/heteroaryl-2*H*-chromen-2-thiones demonstrates the versatility of the annulation protocol via β -oxodithioesters in generating novel biologically important thiocoumarins, as some of them cannot be synthesized easily by traditional classical methods. The tolerance to acid-sensitive reactants such as thienyl and furyl carbaldehydes, applicability to sterically hindered β -oxodithioesters, and simple recyclability without losing catalytic activity make this catalyst a good alternative to literature methods.

Experimental Section

General Methods. All starting materials were commercially available and used as received without further purification. Silica-sulfuric acid was prepared according to the protocol described in literature.^{33b} β -Oxodithioesters **9a–e** were prepared following the known procedure³⁶ displayed in Scheme 2. Thin-layer chromatography (TLC) was performed using silica gel 60 F₂₅₄ precoated plates. Infrared (IR) spectra are measured in KBr, and wavelengths (ν) are reported in cm^{−1}. ¹H and ¹³C NMR spectra were recorded on NMR spectrometers operating at 300 and 75.5 MHz, respectively. Chemical shifts (δ) are given in parts per million (ppm) using the residue solvent peaks as reference relative to TMS. *J* values are given in Hz. Mass spectra were recorded using electrospray ionization (ESI) mass spectrometry. The C, H, and N analyses were performed from micro-analytical laboratory. The melting points are uncorrected.

General Procedure for Synthesis of Dihydropyrimidin-2(1*H*)-ones (12a–v). The β -oxodithioester (1.0 mmol), aldehyde (1.1 mmol), and urea (1.2 mmol) were mixed in a minimum amount of dry ethanol to get a paste like mixture. SiO₂–H₂SO₄ (60 mg) was added to the paste mixture, which was then heated at 80 °C for the stipulated period of time. After completion of the reaction (monitored by TLC), EtOAc (10 mL) was added to

(41) (a) Crystallographic data for compound **12t** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 784530. These data can be obtained free of charge at www.ccdc.cam.ac.uk; (b) Crystallographic data for compound **17a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 783933. These data can be obtained free of charge at www.ccdc.cam.ac.uk.

the reaction mixture and the catalyst was filtered off. Then water (20 mL) was added to the reaction mixture to remove any unreacted urea and the mixture extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhyd Na₂SO₄ and then evaporated in vacuo. The crude residue was purified by column chromatography over silica gel using acetone/dichloromethane (1:99) as eluent to afford pure dihydropyrimidin-2(1H)-ones.

General Procedure for the Synthesis of 2H-Chromene-2-thiones (14a–h). The β-oxodithioester (1.0 mmol), salicylaldehyde (1.2 mmol), urea (1.0 mmol), and SiO₂–H₂SO₄ (60 mg) were mixed and heated at 85 °C for the stipulated period of time. After completion of the reaction (monitored by TLC), ethyl acetate (10 mL) was added to the reaction mixture, and the catalyst was filtered off. Water (20 mL) was then added to the reaction mixture and the mixture extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhyd Na₂SO₄ and then evaporated in vacuo. The crude residue was purified by column chromatography over silica gel using increasing amounts of ethyl acetate in *n*-hexane as eluent to afford 2H-chromene-2-thiones.

General Procedure for the Synthesis of Pyridopyrimidinones (17a–h). To an ethanolic solution of β-oxodithioester (1.0 mmol), aldehyde (1.0 mmol), and 6-amino-1,3-dimethyluracil (1.2 mmol) was added SiO₂–H₂SO₄ (60 mg) and the mixture refluxed for the stipulated period of time. After completion of the reaction (monitored by TLC), the catalyst was filtered out. Ethanol was evaporated; water (20 mL) was added and the mixture extracted by ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhyd Na₂SO₄ and then evaporated in vacuo. The crude residue was purified by column chromatography over silica gel using increasing amounts of ethyl acetate in *n*-hexane as eluent to afford pyridopyrimidinones.

Characterization Data of the Isolated Compounds. 5-Methylmercaptothiocabonyl-4-(4-nitrophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (12a): bright yellow powder; mp 214–215 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 8.20 (d, *J* = 8.7 Hz, 2H), 7.57–7.41 (m, 7H), 7.16 (s, 1H), 6.33 (s, 1H), 6.04 (d, *J* = 2.4 Hz, 1H), 2.30 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, δ ppm) 226.1, 153.1, 148.5, 147.5, 137.9, 133.9, 130.2, 128.8, 128.2, 128.0, 123.9, 118.0, 59.8, 20.5; IR (KBr, ν_{max}, cm^{−1}) 3215, 3076, 1697, 1530; MS *m/z* = 385 (M⁺). Anal. Calcd for C₁₈H₁₅N₃O₃S₂: C, 56.09; H, 3.92; N, 10.90. Found: C, 56.18; H, 3.78; N, 11.01.

5-Methylmercaptothiocabonyl-4-(4-bromophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (12b): bright yellow powder; mp 239–240 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.46–7.37 (m, 8H), 7.27–7.24 (m, 1H), 6.46 (s, 1H), 5.93 (d, *J* = 2.7 Hz, 1H), 5.45 (s, 1H), 2.30 (s, 3H); ¹³C NMR (75 MHz, CDCl₃+DMSO-*d*₆, δ ppm) 224.3, 151.5, 141.0, 140.2, 133.3, 130.1, 128.7, 127.8, 127.3, 119.9, 117.3, 57.8, 19.3; IR (KBr, ν_{max}, cm^{−1}) 3197, 3081, 1697, 1636; MS *m/z* = 418 (M⁺). Anal. Calcd for C₁₈H₁₅BrN₂O₂S₂: C, 51.55; H, 3.61; N, 6.68. Found: C, 51.36; H, 3.77; N, 6.41.

5-Methylmercaptothiocabonyl-4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one (12c): bright yellow powder; mp 196–198 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.45–7.29 (m, 10H), 6.97 (s, 1H), 5.91 (s, 1H), 5.81 (s, 1H), 2.28 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, δ ppm) 227.0, 152.5, 141.6, 136.3, 134.5, 129.8, 128.7, 128.6, 128.1, 127.1, 119.3, 60.9, 20.4; IR (KBr, ν_{max}, cm^{−1}) 3214, 3085, 1698, 1637; MS *m/z* = 340 (M⁺). Anal. Calcd for C₁₈H₁₆N₂O₂S₂: C, 63.50; H, 4.74; N, 8.23. Found: C, 63.33; H, 4.93; N, 8.39.

5-Methylmercaptothiocabonyl-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (12d): bright yellow powder; mp 188–190 °C; ¹H NMR (75 MHz, CDCl₃, δ ppm) 7.46–7.37 (m, 5H), 7.31–7.26 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.32 (s, 1H), 5.89 (d, *J* = 1.5 Hz, 1H), 5.29 (s, 1H), 3.78 (s, 3H), 2.28 (s, 3H); ¹³C NMR (300 MHz, CDCl₃, δ ppm) 227.2, 159.3, 152.5, 136.1,

134.6, 133.9, 129.8, 128.7, 128.4, 128.1, 119.6, 113.9, 60.4, 55.2, 20.4; IR (KBr, ν_{max}, cm^{−1}): 3214, 3078, 1695, 1457; MS *m/z* = 370 (M⁺). Anal. Calcd for C₁₉H₁₈N₂O₂S₂: C, 61.60; H, 4.90; N, 7.56. Found: C, 61.42; H, 5.26; N, 7.76.

5-Methylmercaptothiocabonyl-4-(4-chlorophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (12e): bright yellow powder; mp 250–251 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.45–7.25 (m, 9H), 6.38 (s, 1H), 5.94 (d, *J* = 2.4 Hz, 1H), 5.38 (s, 1H), 2.29 (s, 3H); ¹³C NMR (75 MHz, CDCl₃ + DMSO-*d*₆, δ ppm) 224.3, 151.4, 140.5, 140.2, 133.3, 131.5, 128.6, 127.7, 127.4, 127.2, 127.1, 117.3, 57.6, 19.3; IR (KBr, ν_{max}, cm^{−1}) 3196, 3080, 1696, 1457; MS *m/z* = 374 (M⁺). Anal. Calcd for C₁₈H₁₅ClN₂O₂S₂: C, 56.67; H, 4.03; N, 7.47. Found: C, 56.82; H, 4.30; N, 7.28.

5-Methylmercaptothiocabonyl-4-thienyl-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (12f): bright yellow powder; mp 201–202 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.44–7.41 (m, 5H), 7.03–6.91 (m, 3H), 6.34 (s, 1H), 6.24 (d, *J* = 2.7 Hz, 1H), 5.45 (s, 1H), 2.36 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, δ ppm) 225.1, 152.4, 145.6, 138.1, 134.5, 130.2, 128.9, 128.4, 126.7, 125.5, 125.2, 119.6, 56.0, 20.7; IR (KBr, ν_{max}, cm^{−1}) 3196, 3085, 1695, 1523; MS *m/z* = 346 (M⁺). Anal. Calcd for C₁₆H₁₄N₂O₂S₂: C, 55.46; H, 4.07; N, 8.08. Found: C, 55.23; H, 4.26; N, 8.30.

5-Methylmercaptothiocabonyl-4-(4-bromophenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (12g): bright yellow powder; mp 194–195 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.44–7.34 (m, 4H), 7.26–7.23 (m, 2H), 7.11 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.03 (s, 1H), 5.85 (d, *J* = 2.4 Hz, 1H), 3.82 (s, 3H), 2.32 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, δ ppm) 226.7, 160.9, 152.8, 140.9, 137.6, 131.7, 129.8, 128.8, 126.4, 122.0, 118.3, 114.1, 60.1, 55.3, 20.5; IR (KBr, ν_{max}, cm^{−1}) 3212, 3091, 1697, 1454; MS *m/z* = 448 (M⁺). Anal. Calcd for C₁₉H₁₇BrN₂O₂S₂: C, 50.78; H, 3.81; N, 6.23. Found: C, 50.54; H, 3.67; N, 6.41.

5-Methylmercaptothiocabonyl-4-(4-methoxyphenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (12h): bright yellow powder; mp 203–204 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.39–7.36 (m, 2H), 7.30–7.25 (m, 2H), 6.89–6.82 (m, 4H), 6.32 (s, 1H), 5.86 (d, *J* = 2.1 Hz, 1H), 5.29 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃ + DMSO-*d*₆, δ ppm) 227.3, 160.8, 159.3, 152.4, 136.3, 134.0, 129.6, 128.4, 126.8, 119.2, 114.1, 113.9, 60.5, 55.3, 55.2, 20.4; IR (KBr, ν_{max}, cm^{−1}) 3196, 3096, 1699, 1639; MS *m/z* = 400 (M⁺). Anal. Calcd for C₂₀H₂₀N₂O₃S₂: C, 59.98; H, 5.03; N, 6.99. Found: C, 60.18; H, 5.29; N, 7.26.

5-Methylmercaptothiocabonyl-4-(2-chlorophenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (12i): bright yellow powder; mp 239–241 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.48–7.38 (m, 4H), 7.26–7.23 (m, 2H), 6.95–6.88 (m, 3H), 6.18 (d, *J* = 3.0 Hz, 1H), 5.74 (s, 1H), 3.86 (s, 3H), 2.36 (s, 3H); ¹³C NMR (75 MHz, CDCl₃ + DMSO-*d*₆, δ ppm) 224.7, 160.3, 151.9, 141.2, 138.2, 132.1, 129.7, 129.1, 128.4, 127.8, 126.5, 125.6, 115.6, 113.3, 56.3, 54.5, 19.6; IR (KBr, ν_{max}, cm^{−1}) 3205, 3067, 1703, 1635; MS *m/z* = 404 (M⁺). Anal. Calcd for C₁₉H₁₇ClN₂O₃S₂: C, 56.36; H, 4.23; N, 6.92. Found: C, 56.13; H, 4.19; N, 7.25.

5-Methylmercaptothiocabonyl-4-phenyl-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (12j): bright yellow powder; mp 199–200 °C; ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.39–7.25 (m, 7H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.77 (s, 1H), 5.90 (d, *J* = 1.8 Hz, 1H), 5.63 (s, 1H), 2.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, δ ppm) 227.0, 160.8, 141.9, 137.4, 129.8, 129.3, 128.6, 127.9, 127.1, 126.7, 126.5, 118.7, 114.0, 60.6, 55.2, 20.4; IR (KBr, ν_{max}, cm^{−1}) 3206, 3088, 2193, 1695; MS *m/z* = 370 (M⁺). Anal. Calcd for C₁₉H₁₈N₂O₂S₂: C, 61.60; H, 4.90; N, 7.56. Found: C, 61.88; H, 5.18; N, 7.32.

5-Methylmercaptothiocabonyl-4-thienyl-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (12k): bright yellow powder; mp

176–177 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.39 (d, $J = 8.4$ Hz, 2H), 7.25–7.21 (m, 1H), 7.03 (d, $J = 3.3$ Hz, 1H), 6.94–6.88 (m, 3H), 6.65 (s, 1H), 6.20 (d, $J = 3.3$ Hz, 1H), 5.76 (s, 1H), 3.83 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 224.9, 161.2, 152.7, 145.9, 139.1, 130.0, 126.6, 126.4, 125.3, 125.0, 119.1, 114.3, 55.9, 55.3, 20.7; IR (KBr, ν_{max} , cm^{-1}) 3218, 3065, 1701, 1645; MS $m/z = 376$ (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_3$: C, 54.23; H, 4.28; N, 7.44. Found: C, 54.10; H, 4.42; N, 7.21.

5-Methylmercaptothiocabonyl-4-(3-nitrophenyl)-6-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (12l): bright yellow powder; mp 226–227 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.23 (s, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 7.73 (d, $J = 7.5$ Hz, 1H), 7.54–7.36 (m, 5H), 6.90 (s, 1H), 6.02 (d, $J = 2.4$ Hz, 1H), 5.81 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 224.6, 152.4, 147.6, 144.2, 139.5, 135.5, 132.9, 132.2, 129.9, 128.9, 128.7, 128.3, 127.9, 122.1, 121.6, 117.5, 58.5, 20.0; IR (KBr, ν_{max} , cm^{-1}) 3215, 3078, 1693, 1643; MS $m/z = 419$ (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{ClN}_3\text{O}_3\text{S}_2$: C, 51.49; H, 3.36; N, 10.01. Found: C, 51.63; H, 3.56; N, 10.22.

5-Methylmercaptothiocabonyl-4-(4-methoxyphenyl)-6-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (12m): bright yellow powder; mp 197–198 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.40–7.31 (m, 4H), 7.28 (s, 1H), 6.84–6.81 (m, 4H), 5.84 (s, 1H), 5.51 (s, 1H), 3.78 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 226.6, 158.9, 152.9, 135.8, 135.3, 134.0, 132.7, 129.7, 128.5, 128.1, 119.6, 113.6, 59.7, 54.9, 20.2; IR (KBr, ν_{max} , cm^{-1}) 3197, 3078, 1699, 1640; MS $m/z = 404$ (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_2\text{S}_2$: C, 56.36; H, 4.23; N, 6.92. Found: C, 56.18; H, 4.46; N, 6.73.

5-Methylmercaptothiocabonyl-4-(4-chlorophenyl)-6-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (12n): bright yellow powder; mp 226–227 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.37–7.36 (m, 4H), 7.29–7.25 (m, 4H), 6.53 (s, 1H), 5.90 (d, $J = 2.1$ Hz, 1H), 5.43 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 226.5, 152.6, 139.9, 136.0, 135.2, 134.0, 132.6, 129.5, 129.0, 128.9, 128.5, 119.2, 60.3, 20.4; IR (KBr, ν_{max} , cm^{-1}) 3214, 3085, 2914, 1697; MS $m/z = 408$ (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_2\text{S}_2$: C, 52.81; H, 3.45; N, 6.84. Found: C, 52.66; H, 3.59; N, 6.98.

5-Methylmercaptothiocabonyl-4-(4-chlorophenyl)-6-thienyl-3,4-dihydropyrimidin-2(1H)-one (12o): bright yellow powder; mp 226–227 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.41 (d, $J = 4.5$ Hz, 1H), 7.29–7.25 (m, 5H), 7.03 (t, $J = 4.2$ Hz, 1H), 6.59 (s, 1H), 5.78 (d, $J = 2.1$ Hz, 1H), 5.48 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 226.2, 152.0, 140.3, 134.0, 132.5, 131.5, 128.8, 128.0, 127.9, 127.7, 126.5, 118.7, 58.7, 19.8; IR (KBr, ν_{max} , cm^{-1}) 3076, 1689, 1543; MS $m/z = 380$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}_3$: C, 50.45; H, 3.44; N, 7.35. Found: C, 50.67; H, 3.68; N, 7.10.

5-Methylmercaptothiocabonyl-4-(4-bromophenyl)-6-thienyl-3,4-dihydropyrimidin-2(1H)-one (12p): bright yellow powder; mp 216–217 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.46–7.41 (m, 3H), 7.26–7.22 (m, 3H), 7.03 (t, $J = 4.8$ Hz, 1H), 6.56 (s, 1H), 5.76 (s, 1H), 5.45 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 227.3, 151.8, 140.1, 134.6, 131.8, 129.1, 129.0, 128.9, 128.5, 127.4, 122.4, 119.5, 60.6, 20.6; IR (KBr, ν_{max} , cm^{-1}) 3196, 3089, 1697, 1635; MS $m/z = 424$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{O}_2\text{S}_3$: C, 45.18; H, 3.08; N, 6.59. Found: C, 45.33; H, 3.30; N, 6.32.

5-Methylmercaptothiocabonyl-4-(3-nitrophenyl)-6-thienyl-3,4-dihydropyrimidin-2(1H)-one (12q): bright yellow powder; mp 203–205 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.22 (s, 1H), 8.17 (d, $J = 8.1$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.54–7.44 (m, 2H), 7.29–7.25 (m, 1H), 7.05 (t, $J = 4.8$ Hz, 1H), 6.79 (s, 1H), 5.89 (d, $J = 2.1$ Hz, 1H), 5.82 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 225.3, 151.8, 147.3, 143.9, 133.8, 133.5, 132.8, 129.2, 128.6, 128.3, 126.6, 121.7, 121.4, 117.7, 58.1, 19.8; IR (KBr, ν_{max} , cm^{-1}) 3216, 3086, 1696, 1646; MS $m/z = 391$

(M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3\text{S}_3$: C, 49.09; H, 3.35; N, 10.73. Found: C, 49.35; H, 3.60; N, 10.51.

5-Methylmercaptothiocabonyl-4-phenyl-6-thienyl-3,4-dihydropyrimidin-2(1H)-one (12r): bright yellow powder; mp 178–179 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.40–7.23 (m, 7H), 7.02 (t, $J = 3.6$ Hz, 1H), 6.81 (s, 1H), 5.77 (d, $J = 1.5$ Hz, 1H), 5.60 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 227.6, 153.0, 141.2, 134.7, 129.2, 129.0, 128.6, 128.3, 128.2, 127.3, 127.2, 119.9, 61.0, 20.6; IR (KBr, ν_{max} , cm^{-1}) 3214, 3096, 1696, 1638; MS $m/z = 346$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_3$: C, 55.46; H, 4.07; N, 8.08. Found: C, 55.28; H, 4.28; N, 8.30.

5-Methylmercaptothiocabonyl-4-(2-methoxyphenyl)-6-thienyl-3,4-dihydropyrimidin-2(1H)-one (12s): bright yellow powder; mp 180–181 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.48 (d, $J = 5.4$ Hz, 1H), 7.35–7.33 (m, 2H), 7.08–6.89 (m, 4H), 6.40 (s, 1H), 5.91 (s, 1H), 5.73 (s, 1H), 3.88 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 225.9, 156.1, 134.3, 133.1, 128.8, 128.5, 128.0, 127.9, 126.9, 126.7, 119.6, 117.2, 110.0, 54.7, 54.4, 19.8; IR (KBr, ν_{max} , cm^{-1}) 3083, 2905, 1697, 1634; MS $m/z = 376$ (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_3$: C, 54.23; H, 4.28; N, 7.44. Found: C, 54.41; H, 4.50; N, 7.28.

5-Methylmercaptothiocabonyl-4-(3-nitrophenyl)-6-furyl-3,4-dihydropyrimidin-2(1H)-one (12t): yellow crystals; mp 219–220 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.20–8.14 (m, 2H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.54–7.49 (m, 2H), 7.05 (s, 1H), 6.61 (d, $J = 3.6$ Hz, 1H), 6.46 (d, $J = 1.5$ Hz, 1H), 5.73 (d, $J = 2.1$ Hz, 1H), 5.68 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 224.6, 151.7, 146.8, 144.4, 143.6, 143.0, 132.4, 130.2, 128.2, 121.3, 121.0, 115.6, 112.7, 111.0, 57.3, 19.1; IR (KBr, ν_{max} , cm^{-1}) 3100, 2914, 1698, 1435; MS $m/z = 375$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4\text{S}_2$: C, 51.19; H, 3.49; N, 11.19. Found: C, 51.06; H, 3.64; N, 11.40.

5-Methylmercaptothiocabonyl-4-(4-nitrophenyl)-6-furyl-3,4-dihydropyrimidin-2(1H)-one (12u): bright yellow powder; mp 209–210 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.20 (d, $J = 8.4$ Hz, 2H), 7.55–7.49 (m, 3H), 6.99 (s, 1H), 6.60 (d, $J = 3.0$ Hz, 1H), 6.46 (s, 1H), 5.74 (d, $J = 1.5$ Hz, 1H), 5.60 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 226.2, 152.4, 148.8, 146.8, 144.8, 143.3, 128.6, 127.8, 123.1, 116.4, 112.9, 111.7, 58.8, 19.9; IR (KBr, ν_{max} , cm^{-1}) 3097, 2911, 1697, 1641; MS $m/z = 375$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4\text{S}_2$: C, 51.19; H, 3.49; N, 11.19. Found: C, 51.33; H, 3.23; N, 11.34.

5-Methylmercaptothiocabonyl-4-(4-bromophenyl)-6-furyl-3,4-dihydropyrimidin-2(1H)-one (12v): bright yellow powder; mp 205–206 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.45–7.42 (m, 3H), 7.26–7.21 (m, 3H), 6.59 (d, $J = 3.6$ Hz, 1H), 6.44 (s, 1H), 5.78 (s, 1H), 5.59 (d, $J = 2.1$ Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 228.0, 152.9, 144.8, 143.3, 140.1, 131.7, 129.1, 125.2, 122.3, 117.5, 112.7, 112.1, 60.4, 20.4; IR (KBr, ν_{max} , cm^{-1}) 3212, 3089, 1697, 1637; MS $m/z = 408$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{O}_2\text{S}_2$: C, 46.95; H, 3.20; N, 6.84. Found: C, 46.77; H, 3.36; N, 6.60.

3-Benzoyl-2H-chromene-2-thione (14a): yellow solid; mp 171–172 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.93 (d, $J = 7.8$ Hz, 2H), 7.67–7.35 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 193.5, 192.2, 157.0, 139.2, 135.6, 133.9, 133.5, 133.2, 129.6, 128.7, 128.5, 125.8, 119.9, 116.7; IR (KBr, ν_{max} , cm^{-1}) 3060, 2996, 1673, 1603, 1230; MS $m/z = 266$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{O}_2\text{S}$: C, 72.16; H, 3.78. Found: 72.30; H, 3.95.

3-Benzoyl-8-methoxy-2H-chromene-2-thione (14b): yellow solid; mp 141–143 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.94 (d, $J = 7.5$ Hz, 2H), 7.61–7.58 (m, 2H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.19–7.12 (m, 2H), 4.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 192.8, 192.3, 147.0, 146.7, 139.4, 135.6, 133.8, 133.6, 129.6, 128.7, 125.7, 120.6, 119.5, 114.5, 56.3; IR (KBr, ν_{max} , cm^{-1}) 3085, 3029, 1662, 1601, 1229; MS $m/z = 296$ (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{O}_3\text{S}$: C, 68.90; H, 4.08. Found: 68.72; H, 4.25.

3-(4-Methoxybenzoyl)-6-bromo-2H-chromene-2-thione (14c): yellow solid; mp 206–207 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.91 (d, $J = 9.0$ Hz, 2H), 7.74–7.69 (m, 2H), 7.45 (s, 1H), 7.40 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 192.9, 190.2, 164.4, 155.6, 140.3, 135.6, 132.1, 131.2, 130.5, 128.3, 121.5, 118.4, 118.2, 114.1, 55.5; IR (KBr, ν_{max} , cm^{-1}) 3076, 3031, 1656, 1607, 1235; MS $m/z = 374$ (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{11}\text{BrO}_3\text{S}$: C, 54.41; H, 2.95. Found: C, 54.22; H, 3.15.

3-(4-Methoxybenzoyl)-6-nitro-2H-chromene-2-thione (14d): yellow solid; mp 208–209 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.46 (m, 2H), 7.89 (d, $J = 8.7$ Hz, 2H), 7.63–7.58 (m, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 192.2, 189.6, 164.6, 159.3, 132.1, 130.7, 127.9, 127.3, 123.9, 120.1, 117.6, 114.2, 55.6; IR (KBr, ν_{max} , cm^{-1}) 3051, 1643, 1593, 1236; MS $m/z = 341$ (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{11}\text{NO}_5\text{S}$: C, 59.82; H, 3.25; N, 4.10. Found: C, 59.98; H, 3.06; N, 4.38.

3-(2-Acetylthiophene)-8-methoxy-2H-chromene-2-thione (14e): yellow solid; mp 174–175 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.75 (d, $J = 4.2$ Hz, 1H), 7.65 (d, $J = 3.0$ Hz, 1H), 7.57 (s, 1H), 7.32–7.26 (m, 1H), 7.18–7.11 (m, 3H), 4.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 192.2, 184.3, 146.7, 142.8, 139.0, 135.5, 135.0, 128.3, 125.7, 120.4, 119.5, 114.6, 56.3; IR (KBr, ν_{max} , cm^{-1}) 3059, 2985, 1671, 1602, 1230; MS $m/z = 302$ (M^+). Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{O}_3\text{S}_2$: C, 59.58; H, 3.33. Found: C, 59.73; H, 3.52.

3-(2-Acetylthiophene)-6-bromo-2H-chromene-2-thione (14f): yellow solid; mp 166–167 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.78–7.64 (m, 4H), 7.50 (s, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.15–7.11 (t, $J = 4.2$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 192.4, 183.7, 155.7, 142.5, 139.6, 135.9, 135.1, 131.2, 130.6, 128.4, 121.2, 118.5, 118.2; IR (KBr, ν_{max} , cm^{-1}) 3054, 1676, 1610; MS $m/z = 350$ (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_7\text{BrO}_2\text{S}_2$: C, 47.87; H, 2.01. Found: C, 47.66; H, 2.21.

3-(2-Acetylfuran)-8-ethoxy-2H-chromene-2-thione (14g): yellow solid; mp 175–176 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.61–7.58 (m, 2H), 7.29–7.23 (m, 2H), 7.17–7.10 (m, 2H), 6.57 (d, $J = 1.8$ Hz, 1H), 4.28 (q, $J = 6.9$ Hz, 2H), 1.55–1.53 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 192.7, 179.6, 151.7, 147.4, 146.0, 138.2, 133.8, 125.7, 120.5, 120.1, 119.6, 116.0, 112.7, 65.1, 14.6; IR (KBr, ν_{max} , cm^{-1}) 3085, 3033, 1677, 1600, 1225; MS $m/z = 300$ (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{O}_4\text{S}$: C, 63.99; H, 4.03. Found: C, 64.05; H, 4.32.

3-(2-Acetylfuran)-6-bromo-2H-chromene-2-thione (14h): yellow solid; mp 198–199 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.74–7.62 (m, 2H), 7.51 (s, 1H), 7.39–7.25 (m, 3H), 6.59 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 192.5, 179.0, 155.7, 147.6, 138.9, 136.0, 131.7, 130.7, 121.3, 120.2, 118.5, 118.2, 112.9; IR (KBr, ν_{max} , cm^{-1}) 3076, 3023, 1667, 1606, 1223; MS $m/z = 334$ (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_7\text{BrO}_3\text{S}$: C, 50.17; H, 2.11. Found: C, 50.01; H, 2.28.

6-Methylmercaptothiocabonyl-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-7-phenyl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17a): red crystals; mp 222–223 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.26 (s, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.78 (d, $J = 6.9$ Hz, 1H), 7.50–7.43 (m, 6H), 5.99 (s, 1H), 5.54 (s, 1H), 3.51 (s, 3H), 3.28 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 229.0, 160.9, 150.8, 148.4, 146.5, 143.3, 134.8, 134.0, 130.1, 129.0, 128.9, 128.3, 123.2, 122.6, 121.9, 89.4, 44.3, 28.9, 28.1, 20.4; IR (KBr, ν_{max} , cm^{-1}) 3453, 2961, 1705, 1510; MS $m/z = 480$ (M^+). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_4\text{S}_2$: C, 57.48; H, 4.19; N, 11.66. Found: C, 57.61; H, 4.35; N, 11.42.

6-Methylmercaptothiocabonyl-5-(3-chlorophenyl)-1,3-dimethyl-2,4-dioxo-7-phenyl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17b): Reddish powder; Mp 233–234 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.50–7.37 (m, 6H), 7.32–7.29 (m, 1H), 7.18–7.16 (m, 2H), 5.91 (s, 1H), 5.40 (s, 1H), 3.49 (s, 3H), 3.29 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 229.6, 160.9, 150.9,

146.3, 143.1, 135.1, 134.1, 133.0, 129.9, 129.4, 129.0, 128.2, 127.9, 127.0, 126.5, 124.1, 89.9, 44.3, 28.7, 28.1, 20.5; IR (KBr, ν_{max} , cm^{-1}) 3447, 2954, 1709, 1499; MS $m/z = 469$ (M^+). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{ClN}_4\text{O}_2\text{S}_2$: C, 58.77; H, 4.29; N, 8.94. Found: C, 58.52; H, 4.43; N, 8.72.

6-Methylmercaptothiocabonyl-5-(4-bromophenyl)-7-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17c): reddish powder; mp 205–206 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 7.42–7.36 (m, 4H), 7.30–7.25 (m, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 5.86 (s, 1H), 5.36 (s, 1H), 3.83 (s, 3H), 3.48 (s, 3H), 3.28 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 229.9, 160.9, 160.8, 150.9, 143.5, 143.0, 133.3, 131.3, 129.7, 129.6, 127.2, 123.6, 120.7, 114.4, 90.2, 55.3, 44.0, 28.7, 28.1, 20.5; IR (KBr, ν_{max} , cm^{-1}) 3451, 2934, 1707, 1506; MS $m/z = 543$ (M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{BrN}_3\text{O}_3\text{S}_2$: C, 52.94; H, 4.07; N, 7.72. Found: C, 52.68; H, 4.23; N, 7.50.

6-Methylmercaptothiocabonyl-7-(4-methoxyphenyl)-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17d): reddish powder; mp 240–241 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.24 (s, 1H), 8.05 (d, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 7.5$ Hz, 1H), 7.45–7.41 (m, 3H), 6.93 (d, $J = 8.7$ Hz, 2H), 5.99 (s, 1H), 5.51 (s, 1H), 3.84 (s, 3H), 3.51 (s, 3H), 3.28 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 229.2, 161.0, 150.8, 148.4, 146.7, 143.2, 134.8, 134.4, 129.7, 128.9, 126.9, 122.5, 121.8, 114.5, 89.7, 55.4, 44.2, 28.8, 28.1, 20.5; IR (KBr, ν_{max} , cm^{-1}) 3449, 2934, 1701, 1512; MS $m/z = 510$ (M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_5\text{S}_2$: C, 56.46; H, 4.34; N, 10.97. Found: C, 56.67; H, 4.59; N, 10.71.

6-Methylmercaptothiocabonyl-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-7-thiophen-2-yl-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17e): reddish powder; mp 235–236 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.23 (s, 1H), 8.06 (d, $J = 8.1$ Hz, 1H), 7.75 (d, $J = 7.5$ Hz, 1H), 7.45–7.39 (m, 2H), 7.29–7.28 (m, 1H), 7.06–7.03 (m, 1H), 6.07 (s, 1H), 5.39 (s, 1H), 3.57 (s, 3H), 3.27 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 222.8, 160.9, 146.2, 143.1, 134.8, 129.3, 128.9, 128.4, 127.8, 123.0, 122.7, 122.0, 112.8, 112.6, 89.4, 44.4, 28.7, 28.2, 20.5; IR (KBr, ν_{max} , cm^{-1}) 3441, 2945, 1700, 1503; MS $m/z = 486$ (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_4\text{S}_2$: C, 51.84; 3.73; N, 11.51. Found: C, 51.99; H, 3.98; N, 11.27.

6-Methylmercaptothiocabonyl-7-(4-chlorophenyl)-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17f): reddish powder; mp 257–258 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.23 (s, 1H), 8.06 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 7.5$ Hz, 1H), 7.46–7.37 (m, 5H), 5.89 (s, 1H), 5.51 (s, 1H), 3.51 (s, 3H), 3.27 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$, δ ppm) 228.1, 160.6, 150.5, 147.7, 147.1, 143.7, 136.5, 135.2, 134.1, 132.9, 130.5, 128.5, 128.1, 121.7, 121.5, 121.0, 90.0, 42.9, 29.7, 27.5, 19.9; IR (KBr, ν_{max} , cm^{-1}) 3451, 2961, 1703, 1509; MS $m/z = 514$ (M^+). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{ClN}_4\text{O}_4\text{S}_2$: C, 53.64; H, 3.72; N, 10.88. Found: C, 53.89; H, 3.91; N, 10.68.

6-Methylmercaptothiocabonyl-7-furan-2-yl-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17g): reddish powder; mp 238–239 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.20 (s, 1H), 8.06 (d, $J = 7.8$ Hz, 1H), 7.72 (d, $J = 7.5$ Hz, 1H), 7.51–7.38 (m, 2H), 6.73 (s, 1H), 6.57 (d, $J = 3.3$ Hz, 1H), 6.46 (s, 1H), 5.20 (s, 1H), 3.61 (s, 3H), 3.27 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3 , δ ppm) 230.2, 160.9, 150.8, 148.4, 146.1, 144.5, 143.3, 142.8, 134.7, 128.9, 122.9, 122.6, 122.1, 112.7, 112.6, 88.6, 44.5, 28.6, 28.1, 20.5; IR (KBr, ν_{max} , cm^{-1}) 3447, 2953, 1705, 1505; MS $m/z = 470$ (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_5\text{S}_2$: C, 53.61; H, 3.86; N, 11.91. Found: C, 53.46; H, 3.98; N, 11.72.

6-Methylmercaptothiocabonyl-7-furan-2-yl-1,3-dimethyl-5-(4-nitrophenyl)-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (17h): reddish powder; mp 235–236 °C; ^1H NMR (300 MHz, CDCl_3 , δ ppm) 8.12 (d, $J = 8.4$ Hz, 2H), 7.55–7.51 (m, 3H), 6.71 (s, 1H), 6.57 (d, $J = 3.3$ Hz, 1H), 6.48 (t, $J = 1.5$ Hz,

1H), 5.18 (s, 1H), 3.60 (s, 3H), 3.27 (s, 3H), 2.52 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, δ ppm) 230.1, 160.8, 151.2, 150.8, 146.8, 144.5, 143.3, 142.8, 129.0, 123.6, 122.7, 122.0, 112.7, 112.6, 88.5, 44.6, 28.6, 28.1, 20.5; IR (KBr, ν_{max}, cm⁻¹) 3431, 2951, 1707, 1510; MS *m/z* = 470 (M⁺). Anal. Calcd for C₂₁H₁₈N₄O₅S₂: C, 53.61; H, 3.86; N, 11.91. Found: C, 53.85; H, 3.98; N, 11.63.

Acknowledgment. We great fully acknowledge the generous financial support from Council of Scientific and Industrial

Research (Grant No. 01(2260)/08/EMR-II) and Department of Science and Technology (Grant No. SR/S1/OC-66/2009), New Delhi. G.C.N. and S.S are thankful to CSIR, New Delhi, for senior research fellowship.

Supporting Information Available: Full experimental details; analytical and spectroscopic data (copies of ¹H and ¹³C NMR for compounds **12**, **14**, and **17**); X-ray data for compounds **12t** and **17a** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.