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# The Thorpe–Ziegler-type reaction of 3-cyanopyridine-2(1*H*)-thiones with Biginelli 6-bromomethyl-3,4-dihydropyrimidin-2(1*H*)-ones: cascade assembling of tetra- and pentacyclic heterocyclic scaffolds

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ABSTRACT

3-Cyanopyridine-2(1*H*)-thiones have been shown to react with Biginelli-type ethyl 4-aryl-6-(bromomethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates upon heating in DMF giving rise to ethyl 4-aryl-6-{[(3-cyanopyridin-2-yl)thio]methyl}-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates. The latter upon treatment with an excess of NaH or *t*-BuOK in boiling DMF undergo a tandem Thorpe–Ziegler-type heterocyclization to give pyrido[3″,2″:4′,5′]thieno[2′,3′:5,6]pyrido[4,3-*d*]pyrimidine derivatives in good yields. Selected compounds were tested for antibacterial and antifungal activity.



## 1. Introduction

Cascade reactions, also known as tandem or domino reactions, represent an effective approach for the construction of polycyclic scaffolds. Such reactions allow the efficient synthesis of complex molecules from simple substrates in an ecologically and economically favorable way. Cascade processes offer significant advantages over multistep syntheses due to their flexible and atom efficient nature and have become an important area of research in organic, medicinal, and combinatorial chemistry. A variety of cascade heterocyclization reactions have been investigated to date.[1,2]

For quite some time we have been engaged in the chemistry of methylene active thioamides and their cyclic derivatives—δ-thiolactams and 3-cyano-2-thioxo(mercapto)pyridines. The latter are of a great interest due to their synthetic capabilities and also due to the wide spectrum of biological activity.[3,4] In the past years we have successfully developed some new cascade reactions of 3-cyanopyridine-2(1*H*)-thiones and related 2-thiolates leading to the formation of thieno[2,3-*b*]pyridine derivatives.[5–8] One of the most effective strategies for the synthesis of functionalized thieno[2,3-*b*]pyridines is the use of a two-step sequence of S-alkylation of 3-cyanopyridine-2(1*H*)-thiones→Thorpe–Ziegler-type cyclization.[9] Since both steps require the presence of a base, it seems evident that they could be easily combined in a one-pot tandem process. Such a one-pot approach was also successfully used in the synthesis of tri- and polycyclic heterocyclic ensembles bearing thienopyridine core unit. It has been shown that a number of 1,4-dielectrophilic species have to react with 3-cyanopyridine-2(1*H*)-thiones to give a variety of tricyclic heterocyclic systems. Thus, a series of pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines,[10–12] pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridines,[5–8,13–16] pyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepines,[17] and pyrido[3′,2′:4,5]thieno[3,2-*c*][2,7]naphthyridine[18] were obtained in such a way (Scheme 1).

As a part of our work we attempted to build thieno[2,3-*b*]pyridine based polycyclic ensembles by Thorpe–Ziegler-type reaction between 3-cyanopyridine-2(1*H*)-thiones (**1a**–**j**) and 6-bromomethyl-3,4-dihydropyrimidin-2(1*H*)-ones (6-Br$CH_2$-DHPMs) (**2a**–**e**). The intermediates **3** were expected to be readily transformed into desirable polycyclic ensembles **4** in basic media (Scheme 2). Starting 6-Br$CH_2$-DHPMs **2** are readily available by direct bromination of ethyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates[19–22] and have proven to be effective building blocks

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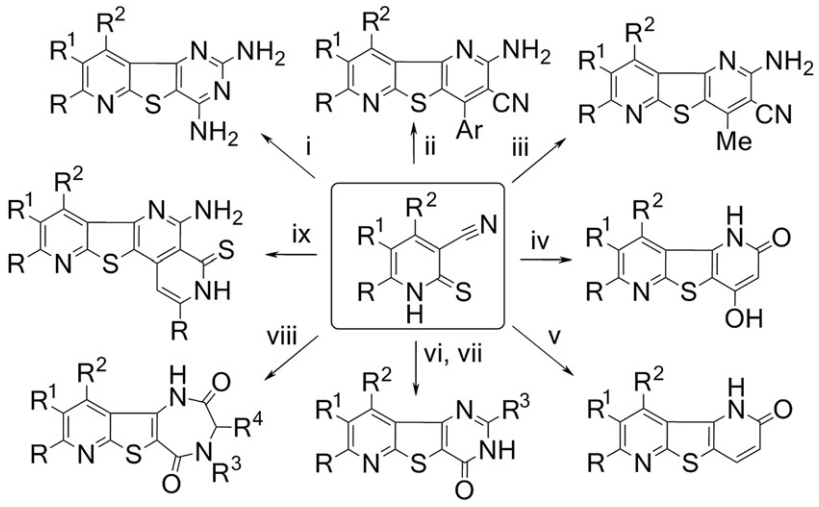
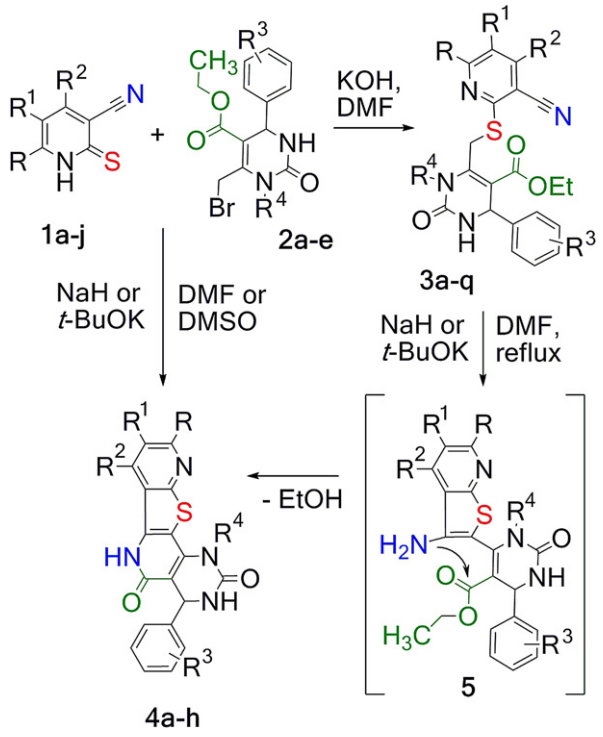


**Scheme 1.** Cascade syntheses of thienopyridine ensembles. (i) $ClCH_2C(=NC{\equiv}N)NH_2$;[10] (ii) $BrCH_2C(Ar){=}C(CN)_2$;[10d,14] (iii) $H_2C(CN)_2$, acetone, *N*-methylmorpholine;[5–8,13] (iv) $ClCH_2C(O)CH_2CO_2Et$;[16] (v) $ClCH_2CH{=}CHCO_2Et$;[15] (vi) $ClCH_2C(O)NHCO_2Et$;[11] (vii) $ClCH_2C(O)NHAc$;[12] (viii) $ClCH_2C(O)N(R^3)CHR^4CO_2Et$;[17] (ix) NBS.[18]



**Scheme 2.** Synthesis of pyrimidine derivatives **3** and **4**.

to construct various heterocyclic systems such as pyrrolo[3,4-*d*]pyrimidines,[20–22] pyrrolo[1,2-*c*]pyrimidines and thiazolo[3,4-*c*]pyrimidines,[23] thiazolo[3,2-*a*]pyrimidines,[24] pyrimido[4,5-*d*]pyridazines,[20,23a] and furo[3,4-*d*]pyrimidines.[25]

## 2. Results/discussion

First, we attempted to synthesize the desired polycycles **4** by direct condensation of pyridine-2(1*H*)-thiones **1** and 6-$BrCH_2$-DHPMs **2**. However, when treated consequently with 1 equiv of 10% KOH and 1 equiv of 6-$BrCH_2$-DHPMs **2a**–**e** upon heating in DMF, pyridine-2(1*H*)-thiones **1a**–**j** undergo regioselective S-alkylation to give ethyl 4-aryl-6-{[(3-cyanopyridin-2-yl)thio]methyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**3a**–**q**) in moderate to excellent yields (50–94%) (Scheme 2, Fig. 1). Surprisingly, treatment of compounds **3** with excessive KOH didn't effect the Thorpe–Ziegler-type reaction and starting materials were recovered mostly unchanged. Thus, when heated with excessive aq KOH in DMF, compound **3i** gave the mixture of starting **3i** (~65%) and cyclization product **4b** (~35%) in 39% overall yield. Usually, the Thorpe–Ziegler cyclization of 2-alkylthio-3-cyanoazines proceeds smoothly under mild conditions in presence of base (AcONa, $Et_3N$, EtONa, aq KOH, etc.) to afford 3-aminothieno[2,3-*b*]azines in good to excellent yields.[9] Moreover, we have previously reported an example of an extremely easy non-catalyzed Thorpe–Ziegler-type thienopyridine synthesis under solvent-free conditions.[26] However, the results we obtained this time were quite disappointing—we failed to effectively promote the cyclization neither by excessive aq KOH, nor by applying other commonly used bases such as $Et_3N$ or AcONa. The attempts to force the cyclization in superbasic media with finely powdered KOH in DMSO led to ambiguous results: though the reaction of 2-thioxoquinoline **1e** with 6-$BrCH_2$-DHPM **2e** readily gave the cyclization product **4c** in 82% yield, in other cases inseparable mixtures were obtained. Finally, we succeeded to synthesize the desirable pyrido[3″,2″:4′,5′]thieno[2′,3′:5,6]pyrido[4,3-*d*]pyrimidines **4** by direct condensation of thiones **1** with 6-$BrCH_2$-DHPMs **2** in the presence of strong bases such as NaH and *tert*-BuOK in dry DMSO (or DMF). Cyclizations of compounds **3** promoted by excessive NaH or potassium *tert*-butoxide were also successful (Scheme 2, Table 1).

Some obstacles were encountered when attempting to obtain compounds **3p** and **3q** by reaction of the corresponding 6-$BrCH_2$-DHPMs **2** with pyridine-2(1*H*)-thione **1j** (Fig. 2). The latter was previously reported to be obtained by condensation of cyanothioacetamide with 2-acetylcyclopentanone.[27] However, at the time current work was in progress, we surprisingly found that compound with suggested structure **1j** prepared by the above method was in fact a mixture of **1j** and isomeric thione **1j′** in ~1:1 ratio.[28] The lack of any significant differences in properties except small chemical shift differences (less than 0.05 ppm) in the $^1H$ NMR spectrum makes the mixture inseparable by physical means. Just as expected, S-alkylations of the mixture **1j**+**1j′** gave the mixtures **3p**+**3p′** and **3q**+**3q′**. Attempts to separate the isomers by common methods such as crystallization or preparative HPLC were also unsuccessful.

All the obtained compounds **3a**–**q** are white or yellowish crystalline solids, soluble in DMSO or hot DMF, sparingly soluble in acetone and AcOH, and insoluble in EtOH. The structures of

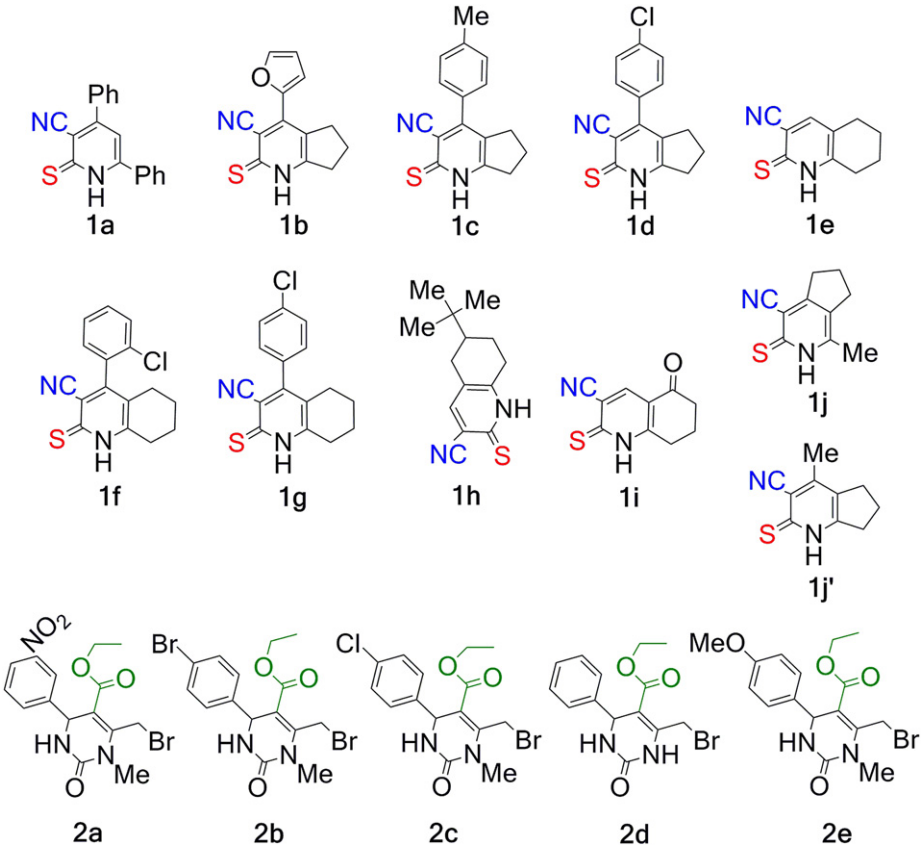



**Fig. 1.** The scope of thiones **1** and 6-Br$CH_2$-DHPMs **2** used.

ethyl 4-aryl-6-{[(3-cyanopyridin-2-yl)thio]methyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**3a**–**q**) were supported by the spectral data as well as the microanalysis data (See Experimental part and Supplementary data for details). Thus, the IR spectra of **3** revealed the presence of conjugated –C≡N group ($\nu$=2215–2230 $cm^{-1}$) and intensive bands of a carbonyl group ($\nu$=1674–1723 $cm^{-1}$). Broad NH bands corresponding to the ureidic N–C(O)–NH fragment appeared at $\nu$=3180–3408 $cm^{-1}$. $^1$H NMR spectra of **3** revealed signals of pyrimidine C(3)NH protons as doublets or broad singlets at $\delta$ 7.84–8.32 ppm and pyrimidine C(4)H as doublets at $\delta$ 5.13–5.40 ppm ($^3J$=2.4–4.0 Hz). Signals of enantiotopic $SCH_2$ protons appeared as two doublets at $\delta$ 4.50–5.09 and 4.62–5.20 ppm ($^2J$=11.6–13.7 Hz). $^1$H NMR spectra also revealed the characteristic picture of aromatic and $CO_2C_2H_5$ protons. The obtained pyrido[3″,2″:4′,5′]thieno[2′,3′:5,6]pyrido[4,3-*d*]pyrimidines **4** are high-melting deep-yellow or brown solids, sparingly soluble in TFA, hot DMSO or DMF, and insoluble in acetone, AcOH or alcohols. The IR spectra of **4** revealed the lack of –C≡N group bands. Instead, broad and intensive bands corresponding to C(O)NH moieties appeared at $\nu$=3375–3419 (N–H) and 1660–1697 (C=O) $cm^{-1}$. $^1$H NMR spectra of **4** revealed no signals corresponding to either $SCH_2$ or $CO_2Et$ fragments. Signals of N(6)H protons are either not observed at all due to H–D exchange, or at the best appeared as very broad peaks at $\delta$ 12.05–12.60 ppm. Signals of C(4)H are shifted somewhat downfield from the corresponding signals in the $^1$H NMR spectra of **3** and appeared mostly as broadened singlets at $\delta$ 5.29–6.15 ppm.

## 3. Antimicrobial activity

Antimicrobial activity of compounds **3a**, **3c**, **3k**, **3l**, **3n**, **3p**+**3p′**, **4a**, and **4e** against the strains of *Staphylococcus aureus* ATCC 25913, *Escherichia coli* M-17, and *Bacillus subtilis* ATCC 6633 as bacteria and *Candida albicans* CCM 885 as fungus was studied in vitro employing the standard Kirby–Bauer disc diffusion method.[29] The obtained results were compared with 16 reference antibiotics and 6 reference antifungal drugs. The tested compounds showed variable antimicrobial activities, which ranged from none to moderate; observations and results are given in Supplementary data. As evidenced from the obtained data, none of the tested compounds revealed significant antibacterial or antifungal activity.

## 4. Conclusions

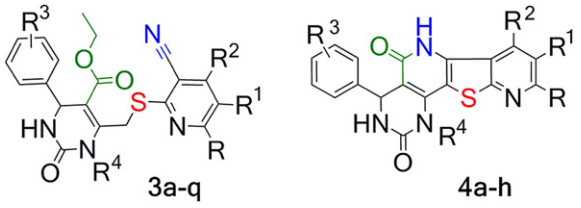
In summary, we have developed an efficient method for the synthesis of functionalized pyrimidine derivatives by reaction of readily available 3-cyanopyridine-2(1*H*)-thiones and 6-bromomethyl Biginelli DHPMs. The products of S-alkylation undergo a new Thorpe–Ziegler-type cascade reaction to give polycyclic ensembles upon being treated with strong bases such as NaH or *t*-BuOK. Certain compounds were tested for antibacterial and antifungal activity and found to be moderately active or inactive toward *S. aureus* ATCC 25913, *E. coli* M-17, *B. subtilis* ATCC 6633. and *C. albicans* CCM 885.

## 5. Experimental section

### 5.1. General

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. Elemental analyses for C, H, and N were conducted using Carlo Erba 1106 elemental analyzer; their results were found to be in good agreement with the calculated values (±0.4%). IR spectra were recorded on an IKS-29 spectrophotometer

**Table 1**
Products **3a**–**q** and **4a**–**h** produced via Scheme 2




| Compound | R | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Isolated yield, % |
|---|---|---|---|---|---|---|
| **3a** | Ph | H | Ph | 3-$NO_2$ | Me | 80 |
| **3b** | $(CH_2)_3$ | | Fur-2-yl | 4-Br | Me | 80 |
| **3c** | $(CH_2)_3$ | | Fur-2-yl | 4-Cl | Me | 94 |
| **3d** | $(CH_2)_3$ | | 4-$MeC_6H_4$ | H | H | 77 |
| **3e** | $(CH_2)_3$ | | 4-$MeC_6H_4$ | 4-Br | Me | 83 |
| **3f** | $(CH_2)_3$ | | 4-$MeC_6H_4$ | 4-Cl | Me | 80 |
| **3g** | $(CH_2)_3$ | | 4-$ClC_6H_4$ | 4-Br | Me | 81 |
| **3h** | $(CH_2)_3$ | | 4-$ClC_6H_4$ | 4-MeO | Me | 84 |
| **3i** | $(CH_2)_4$ | | H | H | H | 57 |
| **3j** | $(CH_2)_4$ | | H | 3-$NO_2$ | Me | 70 |
| **3k** | $(CH_2)_4$ | | H | 4-Br | Me | 86 |
| **3l** | $(CH_2)_4$ | | 2-$ClC_6H_4$ | 4-Br | Me | 72 |
| **3m** | $(CH_2)_4$ | | 4-$ClC_6H_4$ | 4-Br | Me | 81 |
| **3n** | $CH_2CH_2C$(Bu-*t*)$CH_2$ | | H | 4-MeO | Me | 74 |
| **3o** | $(CH_2)_3C(O)$ | | H | 3-$NO_2$ | Me | 75 |
| **3p**+**3p′** | Me | $(CH_2)_3$ | | 4-Br | Me | 56 |
| | $(CH_2)_3$ | | Me | 4-Br | Me | |
| **3q**+**3q′** | Me | $(CH_2)_3$ | | 4-Cl | Me | 50 |
| | $(CH_2)_3$ | | Me | 4-Cl | Me | |
| **4a** | $(CH_2)_4$ | | H | 4-Br | Me | 44 |
| **4b** | $(CH_2)_4$ | | H | H | H | 95 |
| **4c** | $(CH_2)_4$ | | H | 4-MeO | Me | 82 |
| **4d** | $(CH_2)_4$ | | H | 3-$NO_2$ | Me | 81 |
| **4e** | $(CH_2)_3$ | | 4-$MeC_6H_4$ | 4-Br | Me | 35 |
| **4f** | $(CH_2)_3$ | | Fur-2-yl | 4-Br | Me | 65 |
| **4g** | Ph | H | Ph | 3-$NO_2$ | Me | 57 |
| **4h** | $(CH_2)_3$ | | 4-$MeC_6H_4$ | H | H | 54 |

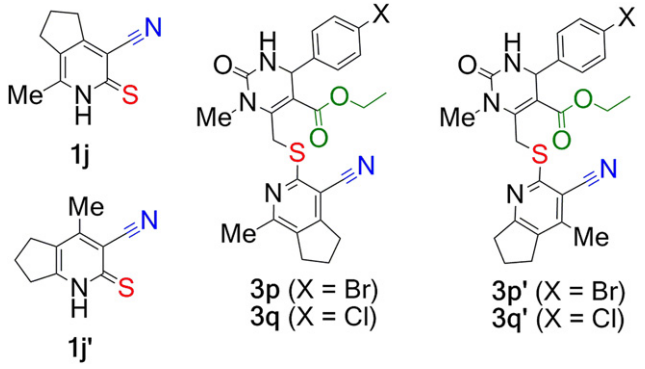



**Fig. 2.** The structures of regioisomeric compounds **1j**+**1j′**, **3p**+**3p′**, and **3q**+**3q′**.

in Nujol mulls, UR-20 spectrophotometer (KBr platelets) (for **4e** and **4f**), and Thermo Nicolet Avatar 370 DTGS model FT-IR Spectrophotometer (KBr) (for **3b**, **3j**, **4a**, and **4d**). The $^1$H NMR spectra were recorded on Varian Unity Plus (400.0 MHz), Bruker DRX-500 (500.1 MHz, $^{13}$C: 125.8 MHz), and Varian Gemini 2000 (400.1 MHz, $^{13}$C: 100.6 MHz) spectrometers in DMSO-$d_6$, $CCl_4$/DMSO-$d_6$ or $CF_3CO_2D$ solutions with $Me_4Si$ as an internal standard. Chemical shifts of protons are reported in parts per million (ppm), coupling constants are reported in hertz (Hz). HPLC/MS analysis was carried out on a system consisting of an Agilent 1100 Series high-pressure liquid chromatograph equipped with DAD and Agilent LC/MSD SL mass-selective detector. HPLC-MS parameters: column: Zorbax SB-C18, 1.8 μm, 4.6×30 mm; injected sample volume: 1 μL; UV detector: λ=215, 254, 265 nm; ionization method: chemical ionization under atmospheric pressure (APCI); ionization mode; simultaneous scanning of positive and negative ions in *m*/*z* range 100–650. Mobile phase: flow in MS: 3 mL/min; A: $CH_3CN$, 1 mL/L HCOOH; B: $H_2O$, 1 mL/L HCOOH; MS parameters: flow in MS: 1 mL/min. Purification of compounds **4e**,**f** was performed on a Shimadzu HPLC system equipped with two LC-8A pumps and an SPD-20A UV detector. The column was a Phenomenex C18 (30×100 mm, packed with 5 μm particles). Mobile phase: gradient elution with MeOH/$H_2O$, starting from 30:70 (v/v) to 100:0, 5 min. The crude product was dissolved in DMSO and then manually injected into the system. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent—Silpearl, large-pore silicagel after Pitra with luminescent indicator for UV 254 on the aluminum foil, binder—starch) in the acetone/hexane (1:1) system; spots were visualized with iodine vapors and UV light.

### 5.2. Synthesis of starting compounds 1 and 2

Starting 4,6-diphenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**1a**) was prepared by known method.[30] 4-(2-Furyl)-2-thioxo-2,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile (**1b**) was obtained by reaction of *N*-(cyclopenten-1-yl)morpholine with (*E*)-2-cyano-3-(2-furyl)prop-2-enethioamide.[31] 4-(4-Methyl phenyl)-2-thioxo-2,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]-pyridine-3-carbonitrile (**1c**) (yield 78%) and 4-(4-chlorophenyl)-2-thioxo-2,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile (**1d**) (yield 69%) were obtained similarly to **1b**, the analytical data matched those reported previously.[32,33] 2-Thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**1e**) was obtained by known procedure.[34] 4-(2-Chlorophenyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**1f**) and 4-(4-chlorophenyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**1g**) were prepared from *N*-(cyclohexen-1-yl)morpholine and (*E*)-3-aryl-2-cyanoprop-2-enethioamide by adopting the same procedure used for the synthesis of **1b**.[31] 5-Oxo-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**1i**) was obtained by reaction of 2-(anilinomethylene)cyclohexane-1,3-dione with cyanothioacetamide by known method.[35] 1-Methyl-3-thioxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridine-4-carbonitrile (**1j**) and 4-methyl-2-thioxo-2,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile (**1j′**) were obtained as ~1:1 mixture by reaction of 2-acetylcyclopentanone with cyanothioacetamide.[28]

*5.2.1. 6-tert-Butyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**1h**).* Compound **1h** was prepared as follows:

(a) *Synthesis of potassium salt of 4-tert-butyl-2-formylcyclohexanone enolate*: A solution of 4-*tert*-butylcyclohexanone (10.0 g, 64.8 mmol, purchased from Acros) and ethyl formate (7.00 mL, 87.0 mmol, dried over $K_2CO_3$) in ether (50 mL, dried over Na) was added dropwise under vigorous stirring to an ice-cold suspension of potassium *tert*-butoxide (7.30 g, 65.0 mmol) in dry ether (100 mL). A slightly exothermic reaction occurs (ice cooling), the mixture thickens and turns yellow. The mixture was stirred for 6 h and left in a freezer at +4 °C for 24 h. The precipitate was filtered off, washed with acetone and ether, dried at 25 °C to give 12.3 g (86%) of the potassium salt of 4-*tert*-butyl-2-formylcyclohexanone enolate as a white powder. The salt was introduced into the next step without further purification.

(b) A mixture of potassium salt of 4-*tert*-butyl-2-formylcyclohexanone enolate (12.3 g, 55.8 mmol) and cyanothioacetamide[28] (5.60 g, 55.9 mmol) in 96% EtOH (25–30 mL) was treated with AcOH (4.0 mL, 70 mmol) and then stirred for 15 min while being slowly heated up to reflux. The mixture was allowed to cool to ambient temperature, the resulting

suspension was stirred for 6 h at 20 °C. The precipitate was filtered off, washed with EtOH to give pure compound **1h** (8.35 g, 61%) as a bright yellow powder; mp 305–310 °C (dec). IR (Nujol): 3195 (NH), 2227 (C≡N), 1605 (C=C); $^1$H NMR (500 MHz, DMSO-$d_6$), ppm: $\delta$=0.90 (9H, s, C($CH_3$)$_3$), 1.23–1.39 (2H, m, $CH_2$), 1.93–1.96 (1H, m, CH), 2.21–2.26 (1H, m, CH), 2.59–2.67 (2H, m, $CH_2$), 2.85–2.89 (1H, m, CH), 7.89 (1H, s, C(4)H), 13.91 (1H, br s, NH); $^{13}$C NMR (125 MHz, DMSO-$d_6$), ppm: $\delta$=22.54, 27.46, 27.66, 28.29, 32.49, 43.25, 113.93, 117.63, 122.32, 146.46, 153.36, 175.87. Anal. Calcd for $C_{14}H_{18}N_2S$ (246.38): C, 68.25; H, 7.36; N, 11.37. Found: C, 68.49; H, 7.46; N, 11.49.

Starting 6-Br$CH_2$-DHPMs **2** were obtained by bromination of ethyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates.[19]

### 5.3. Typical procedure for the synthesis of compounds 3a–s

A suspension of 3-cyanopyridine-2(1*H*)-thione **1** (1.80 mmol) in warm DMF (5 mL) was treated with 10% aq KOH (1.00 mL, 1.95 mmol). After 10 min, 6-bromomethyl-3,4-dihydropyrimidin-2(1*H*)-one **2** (1.80 mmol) was slowly added to the solution. Then the mixture was slowly heated up to reflux, then stirred for 20–30 min at 50–70 °C, allowed to cool, and left overnight. The suspension formed was diluted with ice-cold aq EtOH (15 mL), stirred for 2 h, the precipitated solid was filtered off and washed consequently with EtOH (10 mL), $H_2O$ (10 mL), and EtOH (10 mL) to give compounds **3a**–**s**.

*5.3.1. Ethyl 6-{[(3-cyano-4,6-diphenylpyridin-2-yl)thio]methyl}-1-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**).* White powder, mp 244–246 °C, yield 80%. IR (Nujol): 3180 (NH), 2220 (C≡N), 1723, 1704 (2C=O) cm$^{-1}$; $^1$H NMR (500.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.13 (3H, t, $^3J$ 7.1, $CH_2CH_3$), 3.25 (3H, s, $NCH_3$), 4.04–4.10 (2H, m, $CH_2CH_3$), 5.09 (1H, d, $^2J$ 12.8, SC*H*), 5.20 (1H, d, $^2J$ 12.8, SC*H*), 5.40 (1H, d, $^3J$ 4.0, H-4), 7.56–7.78 (10H, m, H–Ar), 7.99 (1H, s, H-5$_{pyridine}$), 8.17–8.18 (2H, m, H–Ar), 8.32 (1H, d, $^3J$ 4.0, NH), 8.34–8.38 (2H, m, H–Ar); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.7, 28.2, 29.6, 51.8, 60.2, 102.9, 104.4, 115.3, 116.5, 120.9, 122.5, 127.5, 128.5, 128.7, 128.8, 130.0, 130.2, 130.7, 132.5, 135.3, 136.2, 145.2, 147.6, 148.7, 152.5, 154.3, 157.9, 160.8, 164.3; HPLC/MS: 606.2 [M+H]$^+$. Anal. Calcd for $C_{33}H_{27}N_5O_5S$ (605.66): C, 65.44; H, 4.49; N, 11.56. Found: C, 65.38; H, 4.36; N, 11.84.

*5.3.2. Ethyl 4-(4-bromophenyl)-6-({[3-cyano-4-(2-furyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]thio}methyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3b**).* Yellowish solid, mp 208–210 °C (dec), yield 80%. IR (KBr): 3352 (NH), 2221 (C≡N), 1682 (2C=O) cm$^{-1}$; $^1$H NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.12 (3H, t, $^3J$ 6.9, $CH_2CH_3$), 2.06–2.15 (2H, m, $CH_2$), 2.98–3.02 (2H, m, $CH_2$), 3.09–3.12 (2H, m, $CH_2$), 3.19 (3H, s, $NCH_3$), 4.07 (2H, q, $^3J$ 6.9, $CH_2CH_3$), 4.82 (1H, d, $^2J$ 12.4, SC*H*), 4.95 (1H, d, $^2J$ 12.4, SC*H*), 5.14 (1H, d, $^3J$ 3.5, H-4), 6.82–6.83 (1H, m, H-4$_{furyl}$), 7.19 (2H, d, $^3J$ 8.3, H–Ar), 7.32 (1H, d, $^3J$ 3.5, H-3$_{furyl}$), 7.52 (2H, d, $^3J$ 8.3, H–Ar), 8.08 (1H, d, $^3J$ 2.0, H-5$_{furyl}$), 8.14 (1H, d, $^3J$ 3.5, NH); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.8, 21.7, 28.1, 29.6, 31.0, 34.4, 51.8, 60.1, 97.4, 105.0, 112.6, 115.7, 116.0, 120.5, 128.2, 128.9, 131.2, 135.8, 142.5, 145.8, 146.7, 148.0, 152.6, 160.3, 164.5, 170.0; HPLC/MS: 593.2 [M]$^+$. Anal. Calcd for $C_{28}H_{25}BrN_4O_4S$ (593.50): C, 56.66; H, 4.25; N, 9.44. Found: C, 56.72; H, 4.38; N, 9.68.

*5.3.3. Ethyl 4-(4-chlorophenyl)-6-({[3-cyano-4-(2-furyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]thio}methyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3c**).* Yellowish wooly needles, mp 161–162 °C, yield 94%. IR (Nujol): 3180 (NH), 2220 (C≡N), 1723, 1704 (2C=O) cm$^{-1}$; $^1$H NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.12 (3H, t, $^3J$ 7.1, $CH_2CH_3$), 2.09–2.12 (2H, m, $CH_2$), 2.98–3.02 (2H, m, $CH_2$), 3.08–3.12 (2H, m, $CH_2$), 3.19 (3H, s, $NCH_3$), 4.08 (2H, q, $^3J$ 7.1, $CH_2CH_3$), 4.82 (1H, d, $^2J$ 13.0, SC*H*), 4.95 (1H, d, $^2J$ 13.0, SC*H*), 5.17 (1H, d, $^3J$ 3.4, H-4), 6.81–6.82 (1H, m, H-4$_{furyl}$), 7.26 (2H, d, $^3J$ 8.3, H–Ar), 7.31 (1H, d, $^3J$ 3.4, H-3$_{furyl}$), 7.39 (2H, d, $^3J$ 8.3, H–Ar), 8.06–8.07 (1H, m, H-5$_{furyl}$), 8.12 (1H, d, $^3J$ 3.4, NH); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.8, 21.7, 28.1, 29.6, 31.1, 34.3, 51.8, 60.1, 97.4, 105.1, 112.6, 115.6, 116.0, 127.8, 128.3, 128.9, 131.9, 135.8, 142.1, 145.8, 146.7, 148.1, 152.7, 160.3, 164.6, 170.0; HPLC/MS: 549.2 [M+H]$^+$. Anal. Calcd for $C_{28}H_{25}ClN_4O_4S$ (549.05): C, 61.25; H, 4.59; N, 10.20. Found: C, 61.09; H, 4.55; N, 10.45.

*5.3.4. Ethyl 6-({[3-cyano-4-(4-methylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]thio}methyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3d**).* Off-white powder, mp 188–190 °C, yield 77% (yield lowered to 43% when DMF was replaced with EtOH). IR (Nujol): 3230 (NH), 2220 (C≡N), 1722, 1696 (2C=O) cm$^{-1}$; $^1$H NMR (500.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.12 (3H, t, $^3J$=7.1, $CH_2CH_3$), 2.00–2.07 (2H, m, $CH_2$), 2.41 (3H, s, $H_3C$–Ar), 2.79–2.82 (2H, m, $CH_2$), 2.93–3.06 (2H, m, $CH_2$), 4.05 (2H, q, $^3J$ 7.1, $CH_2CH_3$), 4.58 (1H, d, $^2J$ 13.2, SC*H*), 4.62 (1H, d, $^2J$ 13.2, SC*H*), 5.18 (1H, d, $^3J$ 3.4, H-4), 7.24–7.32 (5H, m, Ph), 7.37 (2H, d, $^3J$ 7.8, H–Ar), 7.43 (2H, d, $^3J$ 7.8, H–Ar), 7.84 (1H, br s, *H*N-3), 9.18 (1H, s, *H*N-1); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.8, 20.8, 22.1, 29.3, 34.4, 54.0, 59.6, 101.4, 102.5, 115.6, 126.1, 127.2, 128.2, 129.1, 131.3, 131.9, 139.2, 143.9, 146.5, 149.1, 151.6, 160.3, 164.5, 169.3; HPLC/MS: 525.2 [M+H]$^+$. Anal. Calcd for $C_{30}H_{28}N_4O_3S$ (524.65): C, 68.68; H, 5.38; N, 10.68. Found: C, 68.39; H, 5.45; N, 10.54.

*5.3.5. Ethyl 4-(4-bromophenyl)-6-({[3-cyano-4-(4-methylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]thio}methyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3e**).* Pale yellow solid, mp 151–153 °C (dec, *i*-PrOH/DMF/$H_2O$=2:1:1), yield 83%. IR (Nujol): 3330 (NH), 2218 (C≡N), 1698, 1676 (2C=O) cm$^{-1}$; $^1$H NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.13 (3H, t, $^3J$ 6.8, $CH_2CH_3$), 2.03–2.06 (2H, m, $CH_2$), 2.39 (3H, s, $H_3C$–Ar), 2.78–2.82 (2H, m, $CH_2$), 3.00–3.04 (2H, m, $CH_2$), 3.20 (3H, s, $NCH_3$), 4.08 (2H, q, $^3J$ 6.8, $CH_2CH_3$), 4.83 (1H, d, $^2J$ 12.9, SC*H*), 4.98 (1H, d, $^2J$ 12.9, SC*H*), 5.15 (1H, d, $^3J$ 2.9, H-4), 7.20 (2H, d, $^3J$ 8.1, H–Ar), 7.36 (2H, d, $^3J$ 7.8, H–Ar), 7.42 (2H, d, $^3J$ 7.8, H–Ar), 7.53 (2H, d, $^3J$ 8.1, H–Ar), 8.13 (1H, d, $^3J$ 2.9, NH). Anal. Calcd for $C_{31}H_{29}BrN_4O_3S$ (617.57): C, 60.29; H, 4.73; N, 9.07. Found: C, 60.17; H, 4.75; N, 9.00.

*5.3.6. Ethyl 4-(4-chlorophenyl)-6-({[3-cyano-4-(4-methylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]thio}methyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3f**).* Pale yellow solid, mp 153–155 °C (dec, *i*-PrOH/DMF/$H_2O$=2:1:1), yield 80%. IR (Nujol): 3390 (NH), 2220 (C≡N), 1700, 1678 (2C=O) cm$^{-1}$; $^1$H NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.13 (3H, t, $^3J$ 7.3, $CH_2CH_3$), 2.01–2.08 (2H, m, $CH_2$), 2.39 (3H, s, $H_3C$–Ar), 2.78–2.82 (2H, m, $CH_2$), 3.01–3.05 (2H, m, $CH_2$), 3.20 (3H, s, $NCH_3$), 4.08 (2H, q, $^3J$ 7.3, $CH_2CH_3$), 4.83 (1H, d, $^2J$ 13.4, SC*H*), 4.98 (1H, d, $^2J$ 13.4, SC*H*), 5.17 (1H, d, $^3J$ 3.6, H-4), 7.26 (2H, d, $^3J$ 8.3, H–Ar), 7.36 (2H, d, $^3J$ 8.3, H–Ar), 7.40 (2H, d, $^3J$ 8.3, H–Ar), 7.43 (2H, d, $^3J$ 8.3, H–Ar), 8.13 (1H, d, $^3J$ 3.6, NH); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.8, 20.8, 22.1, 28.0, 29.3, 29.6, 34.6, 51.8, 60.1, 102.7, 105.1, 115.6, 127.8, 128.2, 128.3, 129.1, 131.3, 131.9, 132.0, 139.1, 142.1, 148.0, 149.2, 152.7, 159.2, 164.6, 169.4; HPLC/MS: 573.2 [M+H]$^+$. Anal. Calcd for $C_{31}H_{29}ClN_4O_3S$ (573.12): C, 64.97; H, 5.10; N, 9.78. Found: C, 64.85; H, 5.15; N, 9.70.

*5.3.7. Ethyl 4-(4-bromophenyl)-6-({[4-(4-chlorophenyl)-3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]thio}methyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3g**).* Sand colored powder, mp 153–154 °C (*i*-PrOH/DMF/$H_2O$=2:1:1), yield 81%. IR (Nujol): 3350 (NH), 2220 (C≡N), 1703, 1678 (2C=O) cm$^{-1}$; $^1$H NMR

(400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.18 (3H, t, $^3J$ 6.8, $CH_2CH_3$), 2.07–2.14 (2H, m, $CH_2$), 2.81–2.85 (2H, m, $CH_2$), 3.04–3.08 (2H, m, $CH_2$), 3.21 (3H, s, $NCH_3$), 4.10 (2H, q, $^3J$ 6.8, $CH_2CH_3$), 4.84 (1H, d, $^2J$ 13.7, SC*H*), 4.99 (1H, d, $^2J$ 13.7, SC*H*), 5.15 (1H, d, $^3J$ 3.4, H-4), 7.20 (2H, d, $^3J$ 8.3, H–Ar), 7.47 (2H, d, $^3J$ 8.3, H–Ar), 7.52 (2H, d, $^3J$ 8.3, H–Ar), 7.59 (2H, d, $^3J$ 8.3, H–Ar), 8.11 (1H, d, $^3J$ 3.4, NH); HPLC/MS: 639.0 $[M+H]^+$. Anal. Calcd for $C_{30}H_{26}BrClN_4O_3S$ (637.98): C, 56.48; H, 4.11; N, 8.78. Found: C, 56.59; H, 4.13; N, 8.68.

*5.3.8. Ethyl 6-({[4-(4-chlorophenyl)-3-cyano-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl]thio}methyl)-4-(4-methoxyphenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3h**).* White powder, mp 98–100 °C, yield 84%. IR (Nujol): 3300 (NH), 2220 (C≡N), 1695, 1674 (2C=O) $cm^{-1}$; $^1H$ NMR (399.97 MHz, DMSO-$d_6$), ppm: $\delta$=1.14 (3H, t, $^3J$ 6.8, $CH_2CH_3$), 2.03–2.09 (2H, m, $CH_2$), 2.77–2.81 (2H, m, $CH_2$), 3.03–3.08 (2H, m, $CH_2$), 3.21 (3H, s, $NCH_3$), 3.73 (3H, s, $OCH_3$), 4.07 (2H, q, $^3J$ 6.8, $CH_2CH_3$), 4.84 (1H, d, $^2J$ 11.6, SC*H*), 5.01 (1H, d, $^2J$ 11.6, SC*H*), 5.13 (1H, d, $^3J$ 3.4, H-4), 6.89 (2H, d, $^3J$ 7.7, H–Ar), 7.17 (2H, d, $^3J$ 7.7, H–Ar), 7.59 (2H, d, $^3J$ 7.3, H–Ar), 7.64 (2H, d, $^3J$ 7.3, H–Ar), 8.03 (1H, d, $^3J$ 3.4, NH). Anal. Calcd for $C_{31}H_{29}ClN_4O_4S$ (589.11): C, 63.20; H, 4.96; N, 9.51. Found: C, 63.01; H, 5.00; N, 9.38.

*5.3.9. Ethyl 6-{[(3-cyano-5,6,7,8-tetrahydroquinolin-2-yl)thio]methyl}-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3i**).* Light yellow powder, mp 245–246 °C (dec), yield 57% (yield lowered to 43% when DMF was replaced with EtOH). IR (Nujol): 3391, 3227 (NH), 2221 (C≡N), 1716, 1682 (2C=O) $cm^{-1}$; $^1H$ NMR (500.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.10 (3H, t, $^3J$ 6.8, $CH_2CH_3$), 1.70–1.74 (2H, m, $CH_2$), 1.78–1.81 (2H, m, $CH_2$), 2.69–2.72 (2H, m, $CH_2$), 2.82–2.85 (2H, m, $CH_2$), 4.03 (2H, q, $^3J$ 6.8, $CH_2CH_3$), 4.50 (1H, d, $^2J$ 13.2, SC*H*), 4.57 (1H, d, $^2J$ 13.2, SC*H*), 5.15 (1H, d, $^3J$ 3.5, H-4), 7.20–7.30 (5H, m, Ph), 7.87 (1H, br s, HN-3), 7.97 (1H, s, H-4$_{quinolin-2-yl}$), 9.20 (1H, s, HN-1); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.8, 21.5, 21.7, 26.8, 29.2, 31.9, 54.0, 59.6, 101.1, 103.2, 115.6, 126.1, 127.2, 128.2, 128.9, 141.8, 143.9, 147.1, 151.5, 156.5, 161.5, 164.5; HPLC/MS: 449.3 $[M+H]^+$. Anal. Calcd for $C_{24}H_{24}N_4O_3S$ (448.55): C, 64.27; H, 5.39; N, 12.49. Found: C, 64.15; H, 5.43; N, 12.48.

*5.3.10. Ethyl 6-{[(3-cyano-5,6,7,8-tetrahydroquinolin-2-yl)thio]methyl}-1-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3j**).* White powder, mp 211–212 °C (EtOH/AcOH), yield 70%. IR (KBr): 3408, 3229 (NH), 2221 (C≡N), 1707, 1685 (2C=O) $cm^{-1}$; $^1H$ NMR (500.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.14 (3H, t, $^3J$ 6.9, $CH_2CH_3$), 1.71–1.74 (2H, m, $CH_2$), 1.79–1.81 (2H, m, $CH_2$), 2.70–2.72 (2H, m, $CH_2$), 2.81–2.83 (2H, m, $CH_2$), 3.21 (3H, s, $NCH_3$), 4.10 (2H, q, $^3J$ 6.9, $CH_2CH_3$), 4.86 (1H, d, $^2J$ 13.4, SC*H*), 4.92 (1H, d, $^2J$ 13.4, SC*H*), 5.34 (1H, d, $^3J$ 3.7, H-4), 7.66 (1H, dd, $^3J$ 7.8, 8.3, H–Ar), 7.72 (1H, d, $^3J$ 7.8, H–Ar), 7.93 (1H, s, H-4$_{quinolin-2-yl}$), 8.10 (1H, s, H–Ar), 8.14 (1H, d, $^3J$=8.3, H–Ar), 8.22 (1H, d, $^3J$=3.7, HN); $^{13}C$ NMR (125.8 MHz, DMSO-$d_6$), ppm: $\delta$=14.3, 22.1, 22.4, 27.5, 28.3, 30.4, 32.7, 52.4, 60.8, 104.1, 104.8, 116.2, 121.5, 123.1, 129.6, 130.8, 133.2, 142.5, 146.0, 148.3, 150.0, 153.2, 155.9, 162.2, 165.24. Anal. Calcd for $C_{25}H_{25}N_5O_5S$ (507.57): C, 59.16; H, 4.96; N, 13.80. Found: C, 59.25; H, 5.01; N, 12.88.

*5.3.11. Ethyl 4-(4-bromophenyl)-6-{[(3-cyano-5,6,7,8-tetrahydroquinolin-2-yl)thio]methyl}-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3k**).* Off-white powder, mp 202–204 °C (*i*-PrOH/DMF/$H_2O$=2:1:1), yield 86%. IR (Nujol): 3360 (NH), 2221 (C≡N), 1705, 1677 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.11 (3H, t, $^3J$ 7.1, $CH_2CH_3$), 1.71–1.72 (2H, m, $CH_2$), 1.78–1.80 (2H, m, $CH_2$), 2.68–2.71 (2H, m, $CH_2$), 2.81–2.84 (2H, m, $CH_2$), 3.17 (3H, s, $NCH_3$), 4.06 (2H, q, $^3J$ 7.1, $CH_2CH_3$), 4.80 (1H, d, $^2J$ 13.2, SC*H*), 4.93 (1H, d, $^2J$ 13.2, SC*H*), 5.15 (1H, d, $^3J$ 2.9, H-4), 7.20 (2H, d, $^3J$ 8.3, H–Ar), 7.52 (2H, d, $^3J$ 8.3, H–Ar), 7.93 (1H, s, H-4$_{quinolin-2-yl}$), 8.16 (1H, d, $^3J$ 2.9, HN); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.9, 21.6, 21.9, 27.0, 27.8, 29.8, 32.2, 51.9, 60.1, 103.5, 104.9, 115.6, 120.6, 128.3, 129.0, 131.3, 141.9, 142.6, 148.5, 152.7, 155.3, 161.6, 164.6; HPLC/MS: 543.2 $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}BrN_4O_3S$ (541.46): C, 55.46; H, 4.65; N, 10.35. Found: C, 55.55; H, 4.60; N, 10.48.

*5.3.12. Ethyl 4-(4-bromophenyl)-6-({[4-(2-chlorophenyl)-3-cyano-5,6,7,8-tetrahydroquinolin-2-yl]thio}methyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3l**).* Sand colored powder, mp 215–218 °C (dec, *i*-PrOH/DMF/$H_2O$=2:1:1), yield 72%. IR (Nujol): 3360, 3210 (NH), 2200 (C≡N), 1705, 1682 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.12 (3H, t, $^3J$ 6.8, $CH_2CH_3$), 1.66–1.68 (2H, m, $CH_2$), 1.78–1.82 (2H, m, $CH_2$), 2.18–2.32 (2H, m, $CH_2$), 2.90–2.95 (2H, m, $CH_2$), 3.21 (3H, s, $NCH_3$), 4.07 (2H, q, $^3J$ 6.8, $CH_2CH_3$), 4.84 (1H, d, $^2J$ 13.2, SC*H*), 4.98 (1H, d, $^2J$ 13.2, SC*H*), 5.15 (1H, d, $^3J$ 3.2, H-4), 7.20–7.21 (2H, m, H–Ar), 7.42–7.56 (5H, m, H–Ar), 7.69 (1H, d, $^3J$ 7.3, H–Ar), 8.16 (1H, d, $^3J$ 3.2, HN); HPLC/MS: 653.2 $[M+H]^+$. Anal. Calcd for $C_{31}H_{28}BrClN_4O_3S$ (652.01): C, 57.11; H, 4.33; N, 8.59. Found: C, 57.29; H, 4.40; N, 8.78.

*5.3.13. Ethyl 4-(4-bromophenyl)-6-({[4-(4-chlorophenyl)-3-cyano-5,6,7,8-tetrahydroquinolin-2-yl]thio}methyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3m**).* Off-white powder, mp 194–196 °C (*i*-PrOH/DMF/$H_2O$=2:1:1), yield 81%. IR (Nujol): 3210 (NH), 2220 (C≡N), 1710, 1686 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.13 (3H, t, $^3J$ 7.1, $CH_2CH_3$), 1.64–1.67 (2H, m, $CH_2$), 1.77–1.81 (2H, m, $CH_2$), 2.34–2.37 (2H, m, $CH_2$), 2.90–2.93 (2H, m, $CH_2$), 3.20 (3H, s, $NCH_3$), 4.08 (2H, q, $^3J$ 7.1, $CH_2CH_3$), 4.84 (1H, d, $^2J$ 13.0, SC*H*), 4.99 (1H, d, $^2J$ 13.0, SC*H*), 5.16 (1H, d, $^3J$ 3.7, H-4), 7.21 (2H, d, $^3J$ 8.3, H–Ar), 7.43 (2H, d, $^3J$ 8.3, H–Ar), 7.53 (2H, d, $^3J$ 8.3, H–Ar), 7.61 (2H, d, $^3J$ 8.3, H–Ar), 8.15 (1H, d, $^3J$ 3.7, HN); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.8, 21.5, 21.7, 26.1, 27.6, 29.8, 32.8, 51.8, 60.1, 103.9, 104.9, 114.8, 120.5, 127.0, 128.2, 128.7, 130.0, 131.2, 133.5, 133.9, 142.5, 148.4, 152.5, 152.7, 155.9, 161.4, 164.5. Anal. Calcd for $C_{31}H_{28}BrClN_4O_3S$: C, 57.11; H, 4.33; N, 8.59 (652.01). Found: C, 57.07; H, 4.37; N, 8.48.

*5.3.14. Ethyl 6-{[(6-tert-butyl-3-cyano-5,6,7,8-tetrahydroquinolin-2-yl)thio]methyl}-4-(4-methoxyphenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3n**).* White powder, mp 224–226 °C (dec) (acetone), yield 74%. IR (Nujol): 3240 (NH), 2220 (C≡N), 1710, 1685 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=0.92 (9H, s, $C(CH_3)_3$), 1.12 (3H, t, $^3J$ 6.8, $CH_2CH_3$), 1.36–1.43 (2H, m, C*H*), 2.00–2.02 (1H, m, C*H*), 2.42–2.46 (1H, m, C*H*), 2.77–2.99 (3H, m, C*H*), 3.17 (3H, s, $NCH_3$), 3.73 (3H, s, $OCH_3$), 4.06 (2H, q, $^3J$ 6.8, $CH_2CH_3$), 4.80 (1H, d, $^2J$ 13.2, SC*H*), 4.93 (1H, d, $^2J$ 13.2, SC*H*), 5.12 (1H, d, $^3J$ 2.4, H-4), 6.87 (2H, d, $^3J$ 7.6, H–Ar), 7.16 (2H, d, $^3J$ 7.6, H–Ar), 7.95 (1H, s, H-4$_{quinolin-2-yl}$), 8.01 (1H, br s, HN); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.8, 23.2, 26.9, 27.6, 28.5, 29.6, 31.9, 33.1, 43.1, 51.7, 54.9, 59.9, 103.2, 105.7, 113.6, 115.5, 127.1, 129.0, 135.2, 142.1, 147.6, 152.8, 155.4, 158.4, 161.5, 164.6; HPLC/MS: 549.3 $[M+H]^+$. Anal. Calcd for $C_{30}H_{36}N_4O_4S$ (548.71): C, 65.67; H, 6.61; N, 10.21. Found: C, 65.50; H, 6.54; N, 10.38.

*5.3.15. Ethyl 6-{[(3-cyano-5-oxo-5,6,7,8-tetrahydroquinolin-2-yl)thio]methyl}-1-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3o**), solvate with DMF 1:1.* Off-white powder, mp 120–122 °C (AcOH/DMF), yield 75%. IR (Nujol): 3325 (NH), 2230 (C≡N), 1706–1674 (3C=O) $cm^{-1}$; $^1H$ NMR (500.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.14 (3H, t, $^3J$ 6.9, $CH_2CH_3$), 2.09–2.12 (2H, m, $CH_2$), 2.65–2.68 (2H, m, $CH_2$), 2.74 (3H, s, DMF), 2.90 (3H, s, DMF), 3.08–3.10 (2H, m, $CH_2$), 3.23 (3H, s, $NCH_3$), 4.11 (2H, q, $^3J$ 6.9, $CH_2CH_3$), 4.97 (1H, d, $^2J$ 13.0, SC*H*), 5.04 (1H, d, $^2J$ 13.0, SC*H*), 5.36 (1H, br s, H-4), 7.66–7.69 (1H, m, H–Ar), 7.74 (1H, d, $^3J$ 7.8, H–Ar), 7.96 (1H, s, DMF), 8.11 (1H, s, H–Ar), 8.16 (1H, d, $^3J$ 8.3, H–Ar), 8.31 (1H, br s, HN), 8.49 (1H, s, H-4$_{quinolin-2-yl}$); $^{13}C$ NMR (125.8 MHz, DMSO-$d_6$), ppm: $\delta$=14.3, 21.1, 28.7, 30.5, 31.3, 32.6, 36.3, 37.9, 52.4, 60.9, 105.3, 107.4, 115.3, 121.5, 123.1, 124.8, 130.9, 133.3, 140.3, 145.9, 148.3, 149.3, 153.2, 162.8,

164.4, 165.1, 167.7, 194.6. Anal. Calcd for $C_{25}H_{23}N_5O_6S\times C_3H_7NO$: C, 56.56; H, 5.09; N, 14.13. Found: C, 56.78; H, 5.00; N, 13.98.

*5.3.16. Ethyl 4-(4-bromophenyl)-6-{[(4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio]methyl}-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3p**) and ethyl 4-(4-bromophenyl)-6-{[(3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio]methyl}-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3p′**), mixture **3p**/**3p′** ~2:3.* Light brown powder, mp 195–200 °C (dec, *i*-PrOH/DMF/$H_2O$=2:1:1), yield 56%. IR (Nujol): 3360, 3210 (NH), 2218 (C≡N), 1711, 1681 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, $CCl_4$/DMSO-$d_6$), ppm: $\delta$=1.15* (3H, t, $^3J$ 7.1, $CH_2CH_3$), 2.07–2.17* (2H, m, $CH_2$), 2.38 (3H, s, $CH_3$ (**3p′**)), 2.46 (3H, s, $CH_3$ (**3p**)), 2.86–2.91* (2H, m, $CH_2$), 2.95–3.04* (2H, m, $CH_2$), 3.15 (3H, s, $NCH_3$ (**3p**)), 3.16 (3H, s, $NCH_3$ (**3p′**)), 4.07* (2H, q, $^3J$ 7.1, $CH_2CH_3$), 4.77–4.96* (2H, m, $SCH_2$), 5.12–5.14* (1H, m, H-4), 7.17–7.20* (2H, m, H–Ar), 7.47–7.50* (2H, m, H–Ar), 8.13–8.15* (1H, m, HN). Signals of **3p** and **3p′** overlapped; $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$), ppm: $\delta$=13.9, 17.5, 21.6, 22.3, 23.5, 28.0, 28.3, 29.7, 32.3, 34.4, 51.9, 60.2, 100.6, 104.1, 104.9, 105.1, 114.9, 115.2, 120.5, 128.3, 131.3, 133.0, 135.5, 142.6, 147.8, 148.2, 148.5, 152.7, 155.8, 157.3, 158.2, 159.2, 164.6, 164.7, 168.4; HPLC/MS: 541.1 $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}BrN_4O_3S$ (541.46): C, 55.46; H, 4.65; N, 10.35. Found: C, 55.60; H, 4.69; N, 10.50.

*5.3.17. Ethyl 4-(4-chlorophenyl)-6-{[(4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio]methyl}-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3q**) and ethyl 4-(4-chlorophenyl)-6-{[(3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio]methyl}-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3q′**), **3q**/**3q′** ratio is not defined*.* Sand-gray colored powder, mp 182–188 °C (dec, DMF), yield 50%. IR (Nujol): 3220 (NH), 2215 (C≡N), 1704, 1680 (2C=O) $cm^{-1}$; $^1H$ NMR* (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.08–1.16 (6H, m, $2CH_2CH_3$), 2.00–2.15 (4H, m, $2CH_2$), 2.30–2.42 (6H, m, $2CH_3$), 2.80–2.90 (4H, m, $2CH_2$), 2.91–2.99 (4H, m, $2CH_2$), 3.15–3.16 (6H, m, $2NCH_3$), 4.00–4.13 (4H, m, $2CH_2CH_3$), 4.77–4.84 (2H, m, 2SCH), 4.90–4.98 (2H, m, 2SCH), 5.15–5.18 (2H, m, 2H-4), 7.20–7.29 (4H, m, H–Ar), 7.34–7.40 (4H, m, H–Ar), 8.10–8.13 (2H, m, 2HN); $^{13}C$ NMR* (125.8 MHz, $CF_3CO_2D$), ppm: $\delta$=12.1, 16.8, 18.1, 21.4, 21.6, 23.2, 28.8, 29.0, 30.0, 31.8, 34.3, 35.3, 52.5, 52.9, 64.0, 64.2, 100.4, 100.6, 105.3, 115.2, 126.3, 127.4, 127.5, 129.16, 129.24, 135.7, 142.0, 146.2, 146.5, 153.6, 154.5, 155.9, 159.8, 163.8, 163.9, 170.4. Anal. Calcd for $C_{25}H_{25}ClN_4O_3S$ (497.01): C, 60.41; H, 5.07; N, 11.27. Found: C, 60.60; H, 5.12; N, 11.15.

*As the mixture was poorly soluble in the majority of commonly used NMR solvents including DMSO-$d_6$ and deuterated TFA, the product's spectra were not resolved though the signals were quite suitable to confirm the structure.

### 5.4. Synthesis of compounds 4

3-Cyanopyridine-2(1*H*)-thione **1** (0.500 mmol) was dissolved in dry DMSO (3–4 mL) at 40 °C and treated with excess of sodium hydride (60% dispersion in mineral oil, 80.0–120.0 mg, 2.0–3.0 mmol). After 10 min, 6-$BrCH_2$-DHPM **2** (0.550 mmol) was added to the thiolate solution. The mixture was stirred for 15 min while being slowly heated up to reflux, stirred for another 20–30 min at 50 °C, allowed to cool to room temperature, and left overnight. The suspension formed was diluted with ice-cold aq EtOH (20 mL), treated with an excess of AcOH (5 mL) and stirred for 2 h. The precipitate was filtered off, then washed with EtOH (10 mL), $H_2O$ (10 mL), and EtOH (10 mL) to give compounds **4a**,**e**,**f**.

*5.4.1. 4-(4-Bromophenyl)-1-methyl-4,6,8,9,10,11-hexahydropyrimido[4″,5″:4′,5′]pyrido[2′,3′:4,5]thieno[2,3-b]quinoline-2,5(1H,3H)-dione (**4a**).* Deep-yellow powder, mp >250 °C (*i*-PrOH/DMF/$H_2O$=2:1:1), yield 44%. IR (KBr): 3394 (2NH), 1697 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, $CCl_4$/DMSO-$d_6$ ~1:3), ppm: $\delta$=1.79–1.87 (2H, m, $CH_2$), 1.87–1.94 (2H, m, $CH_2$), 2.87–2.93 (2H, m, $CH_2$), 2.94–3.00 (2H, m, $CH_2$), 3.59 (3H, s, $NCH_3$), 5.46 (1H, br s, H-4), 7.33 (2H, d, $^3J$ 7.8, H–Ar), 7.46 (2H, d, $^3J$ 7.8, H–Ar), 8.16 (1H, br s, *H*N-3), 8.44 (1H, s, H-7), 12.63* (1H, very br s, *H*N-6). *Partially exchanged. $^1H$ NMR (400.1 MHz, $CF_3CO_2D$), ppm: $\delta$=2.08–2.13 (2H, m, $CH_2$), 2.14–2.20 (2H, m, $CH_2$), 3.22–3.28 (2H, m, $CH_2$), 3.39–3.45 (2H, m, $CH_2$), 3.97 (3H, s, $NCH_3$), 5.96 (1H, br s, H-4), 7.32 (2H, d, $^3J$ 7.6, H–Ar), 7.51 (2H, d, $^3J$ 7.6, H–Ar), 9.11 (1H, s, H-7). Signals of NH protons were not detected due to chemical exchange; $^{13}C$ NMR (100.6 MHz, $CCl_4$/DMSO-$d_6$ ~1:3), ppm: $\delta$=22.2, 22.4, 28.5, 71.8, 32.58, 50.2, 120.4, 128.0, 129.0, 130.1, 131.1, 142.2, 144.0, 153.7, 156.4, 158.7, 159.7; HPLC/MS: 497.0 $[M+H]^+$. Anal. Calcd for $C_{23}H_{19}BrN_4O_2S$ (495.39): C, 55.76; H, 3.87; N, 11.31. Found: C, 55.53; H, 3.92; N, 11.45.

*5.4.2. 4-Phenyl-4,6,8,9,10,11-hexahydropyrimido[4″,5″:4′,5′]pyrido[2′,3′:4,5]thieno[2,3-b]quinoline-2,5(1H,3H)-dione (**4b**).* Potassium *tert*-butoxide (82.0 mg, 0.73 mmol) was added to a stirred suspension of compound **3i** (105.0 mg, 0.23 mmol) in dry DMSO (1.5 mL). The mixture was stirred for 2 h at 70 °C, allowed to cool to room temperature, and left overnight. The suspension formed was diluted with ice-cold aq EtOH (10 mL), treated with an excess of AcOH (3 mL) and stirred for 2 h. The precipitate formed was filtered off, then washed with EtOH, $H_2O$ and hot EtOH to give **4b** (77 mg, 82%), light brown powder, mp >250 °C. The yield was increased to 95% when NaH (60% in oil, ~10 mol equiv) was used as a base. IR (Nujol): 3375–3330 (3NH), 1692 (2C=O) $cm^{-1}$; $^1H$ NMR (399.97 MHz, $CCl_4$/DMSO-$d_6$ ~1:3), ppm: $\delta$=1.75–1.82 (2H, m, $CH_2$), 1.83–1.90 (2H, m, $CH_2$), 2.86–2.88 (2H, m, $CH_2$), 2.95–2.98 (2H, m, $CH_2$), 5.46 (1H, d, $^3J$ 2.5, H-4), 7.23–7.40 (5H, m, Ph), 7.94 (1H, br s, *H*N-3), 8.41 (1H, s, H-7), 10.07 (1H, br s, *H*N-1), 12.52 (1H, br s, *H*N-6). Anal. Calcd for $C_{22}H_{18}N_4O_2S$ (402.47): C, 65.65; H, 4.51; N, 13.92. Found: C, 65.88; H, 4.62; N, 13.85.

*5.4.3. 4-(4-Methoxyphenyl)-1-methyl-4,6,8,9,10,11-hexahydropyrimido[4″,5″:4′,5′]pyrido[2′,3′:4,5]thieno[2,3-b]quinoline-2,5(1H,3H)-dione (**4c**).* Finely powdered KOH (516 mg, 9.20 mmol) was kept under gentle reflux in DMSO (3.5 mL) under vigorous stirring to obtain a stable suspension. 2-Thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile **1e** (321 mg, 1.69 mmol) and ethyl 6-(bromomethyl)-4-(4-methoxyphenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **2e** (653 mg, 1.70 mmol) were added in succession. The mixture was stirred for 15 min while being slowly heated up to reflux, allowed to cool and then stirred for 4 h at 20 °C. The almost black solution formed was treated with an excess of glacial AcOH (~5 mL) and aq EtOH (~5 mL), and left for 2 days at 20 °C. The precipitate formed was filtered off and then washed with EtOH, $H_2O$, and hot EtOH to give **4c** (616 mg, 82%) as sand-gray powder, mp >300 °C. IR (Nujol): 3395 (2NH), 1693 (2C=O) $cm^{-1}$; $^1H$ NMR (500.1 MHz, DMSO-$d_6$), ppm: $\delta$=1.84–1.88 (2H, m, $CH_2$), 1.90–1.95 (2H, m, $CH_2$), 2.91–2.95 (2H, m, $CH_2$), 2.97–3.04 (2H, m, $CH_2$), 3.62 (3H, br s, $NCH_3$), 3.75 (3H, br s, $OCH_3$), 5.49 (1H, br s, H-4), 6.83–6.93* (2H, m, H–Ar), 7.25–7.35* (2H, m, H–Ar), 7.76 (1H, br s, *H*N-3), 8.46 (1H, s, H-7), 12.05 (1H, very br s, *H*N-6). *Unresolved; $^1H$ NMR (400.1 MHz, $CF_3CO_2D$), ppm: $\delta$=2.08–2.12 (2H, m, $CH_2$), 2.15–2.19 (2H, m, $CH_2$), 3.23–3.26 (2H, m, $CH_2$), 3.40–3.44 (2H, m, $CH_2$), 3.95 (3H, m, $NCH_3$), 3.99 (3H, m, $OCH_3$), 5.96 (1H, br s, H-4), 7.02 (2H, d, $^3J$ 8.3, H–Ar), 7.39 (2H, d, $^3J$ 8.3, H–Ar), 9.14 (1H, s, H-7). Signals of NH protons were not detected due to chemical exchange; $^{13}C$ NMR (100.6 MHz, $CF_3CO_2D$), ppm: $\delta$=10.6, 11.0, 18.1, 19.3, 22.9, 42.1, 45.8, 99.6, 100.7, 102.4, 105.5, 109.2, 115.5, 118.2, 123.6, 125.7, 126.3, 129.9, 138.1, 139.1, 146.3,

148.5, 149.2, 150.8; HPLC/MS: 447.2 $[M+H]^+$. Anal. Calcd for $C_{24}H_{22}N_4O_3S$ (446.52): C, 64.56; H, 4.97; N, 12.55. Found: C, 64.69; H, 5.01; N, 12.67.

*5.4.4. 1-Methyl-4-(3-nitrophenyl)-4,6,8,9,10,11-hexahydropyrimido[4″,5″:4′,5′]pyrido[2′,3′:4,5]thieno[2,3-b]quinoline-2,5(1H,3H)-dione (**4d**).* A 25 mL beaker was charged with sodium hydride (254 mg, 6.35 mmol, 60% dispersion in mineral oil) and dry DMF (5 mL). After 2 min, a suspension of compound **3j** (300 mg, 0.59 mmol) in dry DMF (5 mL) was added. The dark brown mixture was kept under gentle reflux for 10 min. The obtained slurry was treated with AcOH (10 mL), stirred at ambient temperature for 2 h. The precipitate formed was filtered off and washed with hot EtOH, $H_2O$, and acetone to give **4d** (220 mg, 81%) as deep brown powder, mp >250 °C. IR (KBr): 3419 (2NH), 1638 (2C=O, C=C) $cm^{-1}$; $^1H$ NMR* (400.1 MHz, $CF_3CO_2D$), ppm: $\delta$=2.10–2.19 (2H, m, $CH_2$), 2.20–2.25 (2H, m, $CH_2$), 3.23–3.30 (2H, m, $CH_2$), 3.50–3.54 (2H, m, $CH_2$), 4.48 (3H, s, $NCH_3$), 6.15 (1H, br s, H-4), 7.86–7.96 (2H, m, H–Ar), 8.65–8.72 (2H, m, H–Ar), 9.17 (1H, s, H-7). Signals of NH protons were not detected due to chemical exchange. *Poorly resolved. The compound is almost insoluble in any common NMR solvent; HPLC/MS: 462.2 $[M+H]^+$. Anal. Calcd for $C_{23}H_{19}N_5O_4S$ (461.49): C, 59.86; H, 4.15; N, 15.18. Found: C, 59.59; H, 4.25; N, 15.37.

*5.4.5. 4-(4-Bromophenyl)-1-methyl-7-(4-methylphenyl)-4,8,9,10-tetrahydro-1H-cyclopenta-[5″,6″]pyrido[3″,2″:4′,5′]thieno[2′,3′:5,6]pyrido[4,3-d]pyrimidine-2,5(3H,6H)-dione (**4e**).* Yellow powder, mp >250 °C, yield 35%. The compound was purified by preparative HPLC. IR (KBr): 3375 (2NH), 1695 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, DMSO-$d_6$), ppm: $\delta$=2.09–2.16 (2H, m, $CH_2$), 2.48 (3H, s, $CH_3$), 2.68–2.87 (2H, m, $CH_2$), 3.11–3.15 (2H, m, $CH_2$), 3.62 (3H, s, $NCH_3$), 5.29 (1H, d, $^3J$ 3.7, H-4), 7.24 (2H, d, $^3J$ 8.3, H–Ar), 7.33–7.48 (6H, m, H–Ar), 8.26 (1H, d, $^3J$ 3.7, *H*N-3). Signal of *H*N-6 proton was not detected due to chemical exchange; HPLC/MS: 571.1 $[M+H]^+$. Anal. Calcd for $C_{29}H_{23}BrN_4O_2S$ (571.49): C, 60.95; H, 4.06; N, 9.80. Found: C, 60.71; H, 4.11; N, 9.97.

*5.4.6. 4-(4-Bromophenyl)-7-(2-furyl)-1-methyl-4,8,9,10-tetrahydro-1H-cyclopenta[5″,6″]pyrido[3″,2″:4′,5′]thieno[2′,3′:5,6]pyrido[4,3-d]pyrimidine-2,5(3H,6H)-dione (**4f**).* Deep brown powder, mp >250 °C, yield 65%. The compound was purified by preparative HPLC. IR (KBr): 3400 (2NH), 1683 (2C=O) $cm^{-1}$; $^1H$ NMR (400.1 MHz, $CCl_4$/DMSO-$d_6$ ~1:3), ppm: $\delta$=2.18–2.22 (2H, m, $CH_2$), 2.92–3.15 (4H, m, 2 $CH_2$), 3.64 (3H, s, $NCH_3$), 5.44 (1H, d, $^3J$ 3.7, H-4), 6.83 (1H, dd, $^3J$ 3.4, $^3J$ 3.4, H-$4_{furyl}$), 7.13 (1H, d, $^3J$ 3.4, H-$3_{furyl}$), 7.31 (2H, d, $^3J$ 8.3, H–Ar), 7.47 (2H, d, $^3J$ 8.3, H–Ar), 8.00–8.01 (1H, m, H-$5_{furyl}$), 8.24 (1H, d, $^3J$ 3.7, *H*N-3). Signal of *H*N-6 proton was not detected due to chemical exchange; HPLC/MS: 549.0 $[M+H]^+$. Anal. Calcd for $C_{26}H_{19}BrN_4O_3S$ (547.42): C, 57.05; H, 3.50; N, 10.23. Found: C, 56.83; H, 3.61; N, 10.01.

*5.4.7. 1-Methyl-4-(3-nitrophenyl)-7,9-diphenyl-4,6-dihydropyrido[3″,2″:4′,5′]thieno[2′,3′:5,6]pyrido[4,3-d]pyrimidine-2,5(1H,3H)-dione (**4g**).* A 25 mL beaker was charged sodium hydride (230 mg, 5.75 mmol, 60% dispersion in mineral oil) and dry DMF (3 mL). After 2 min, a hot solution of compound **3a** (300 mg, 0.495 mmol) in dry DMF (3 mL) was added. The dark brown mixture was kept under gentle reflux for 5–6 min. The obtained slurry was treated with AcOH (10 mL) and stirred for 2 h at room temperature. The precipitate formed was filtered off and washed with hot EtOH, $H_2O$, and acetone to give **4g** (157 mg, 57%) as brown powder, mp >250 °C. IR (Nujol): 3390 (2NH), 1635 (2C=O, C=C) $cm^{-1}$; $^1H$ NMR (400.1 MHz, $CCl_4$/DMSO-$d_6$ ~1:3), ppm: $\delta$=3.66 (3H, s, $NCH_3$), 5.50 (1H, m, H-4), 7.47–8.23 (16H, m, H–Ar, H-8, *H*N-3), 12.56 (1H, br s, *H*N-6). Anal. Calcd for $C_{31}H_{21}N_5O_4S$ (559.60): C, 66.54; H, 3.78; N, 12.52. Found: C, 66.33; H, 3.86; N, 12.71.

*5.4.8. 7-(4-Methylphenyl)-4-phenyl-4,8,9,10-tetrahydro-1H-cyclopenta[5″,6″]pyrido[3″,2″:4′,5′]thieno[2′,3′:5,6]pyrido[4,3-d]pyrimidine-2,5(3H,6H)-dione (**4h**).* A 10 mL round-bottom flask was charged with sodium hydride (264 mg, 6.60 mmol, 60% dispersion in mineral oil) and dry DMF (2 mL). After 2 min, a hot suspension of **3d** (346 mg, 0.66 mmol) in dry DMF (3 mL) was added. The mixture was gently heated at reflux for 2 h. The obtained slurry was poured into EtOH (20 mL) in a 50 mL beaker, treated with concd HCl (3 mL) and left for 24 h. The obtained solid was filtered off and washed with hot EtOH (10 mL), $H_2O$ (10 mL), and hot acetone (10 mL) to give **4h** (170 mg, 54%) as deep-yellow powder, mp >250 °C. IR (Nujol): 3360 (2NH), 1660 (2C=O) $cm^{-1}$; $^1H$ NMR* (400.1 MHz, $CF_3CO_2D$), ppm: $\delta$=2.50–2.65 (7H, m, $CH_3$, 2 $CH_2$), 3.20–3.30 (2H, m, $CH_2$), 4.10 (3H, s, $NCH_3$), 5.95 (1H, br s, H-4), 7.39–7.78 (9H, m, H–Ar). Signals of NH protons were not detected due to chemical exchange. *Poorly resolved. The compound is almost insoluble in any common solvent; HPLC/MS: 477.0 $[M-H]^-$. Anal. Calcd for $C_{28}H_{22}N_4O_2S$ (478.57): C, 70.27; H, 4.63; N, 11.71. Found: C, 70.02; H, 4.70; N, 11.90.

### 5.5. Antimicrobial studies

The tested compounds **3a**, **3c**, **3k**, **3l**, **3n**, **3p**+**3p′**, **4a**, and **4e** were dissolved in DMF to obtain a 1.0 mg/mL solutions. The sterile 6-mm filter paper discs (HardyDisks AST™) were impregnated by the solutions to obtain the samples containing about 10 μg of compound per disk and then were dried for 72 h at 60 °C. The inoculum for the experiments was prepared fresh in Mueller–Hinton broth from preserved frozen slants. It was incubated at 37 °C for 20 h, a suspension of the colonies with 0.85 per cent normal saline was made, turbidity adjusted to 0.5 McFarland. Mueller–Hinton agar plates were prepared aseptically to get a thickness of 4.0±0.5 mm. The plates were allowed to solidify and were dried at 35–37 °C for 10–20 min before inoculation. The cultures were inoculated in the prepared plates, the sterile discs containing test antibiotics, standard, and blank ones were placed on the previously inoculated surface of the Mueller–Hinton agar plate. The inhibition zones were measured in millimeters at the end of an incubation period of 18–24 h at 35–37 °C. DMF alone showed no inhibition zone. The measurements of the bacteria or fungi growth inhibition were performed with Hi Antibiotic Zone Scale (HiMedia). The discs with reference medications were purchased from HardyDisks AST™.

## Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.041.

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