[γ-Fe_2O_3@HAp-SO_3H] an efficient nanocatalyst for the synthesis of highly functionalised 2-thioxopyrido[2,3-*d*]pyrimidines

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HAp(hydroxyapatite)-encapsulated-γ-Fe_2O_3 supported sulfonic acid nanoparticles were used for the preparation of two series of 2-thioxopyrido[2,3-*d*]pyrimidines. In the first series, 2-thioxopyrido[2,3-*d*]pyrimidines were synthesised from 3-(6-amino-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidin-5-yl)-3-oxopropanenitrile and arylaldehydes in the presence of [γ-Fe_2O_3@HAp-SO_3H] as a nanocatalyst, in high yields (84–96%). In the second series, [γ-Fe_2O_3@HAp-SO_3H] was used to catalyse the reaction of 6-amino-2-(alkylthio)-pyrimidine-4,6(1*H*,5*H*)-dione, 1,3-diethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione and various arylaldehydes to prepare 2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:5,6-*d*']dipyrimidine-4,6 (1*H*,5*H*)-diones in excellent yields (93–98%).

Keywords: nanocatalyst, magnetic nanoparticles, 2-thioxopyridopyrimidine, 6-aminothiouracil, cyanopyrido[2,3-*d*]pyrimidine-5-one, thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione

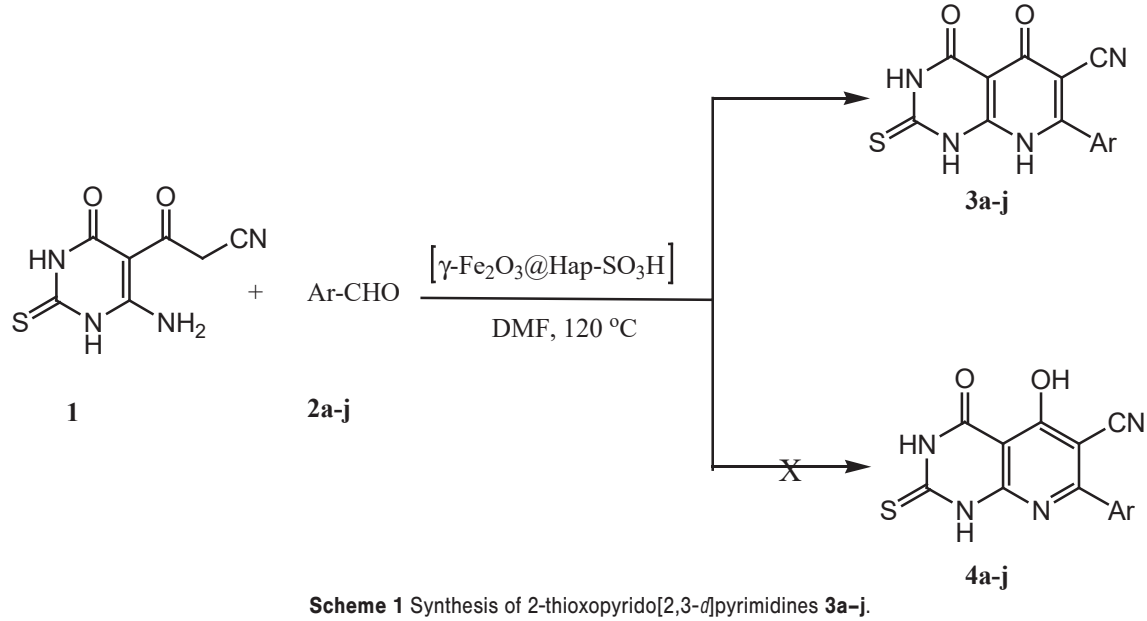
In recent years, heterogeneous catalysts have been extensively employed to speed up organic reactions. The key advantages of these catalysts are environmental compatibility, operational simplicity, nontoxicity, easy of separation from the reaction mixture and low cost.[1,2] The efficiency of heterogeneous catalysis in organic synthesis can be improved by employing nano scale catalysts because nanoparticles have a high specific surface area, leading to an increase of contact with the reactants.[3] They generally exhibit higher catalytic activity than conventional heterogeneous acid catalysts. One particularly useful and important group of nanoparticles is magnetic nanoparticles.

Because of versatile biological and medicinal properties of pyridopyrimidines, their synthesis has attracted the interest of many organic chemists. The pyrido[2,3-*d*]pyrimidine structural moeity is found in a large number of pharmaceutical agents which exhibit a diverse range of physiological activities such as antibacterial,[4] antiviral,[5] diuretic, analgesic,[6] anticonvulsive,[7,8] antipyretic,[9] anti-inflammatory,[10] antitumoral,[11] antihistaminic,[12] cardiotonic,[13,14] and bactericidal.[15] They also have bronchiodilator[16] activity and can act as a cyclin-dependent kinase 4 inhibitor.[17]

Recently, due to the unique properties of nanomaterials,[18–20] synthetic chemists have focused on the synthesis of organic compounds using nanocatalysts. Synthesis of pyridopyrimides by employing nanocatalysts has also been reported.[21,22] In continuation of our recent work using sulfonic acid-functionalised nano-Fe_2O_3 particles [γ-Fe_2O_3@HAp-SO_3H] as a magnetic Brønsted efficient acid catalyst to synthesise pyridopyrimidines,[23] we decided to investigate synthesis of the another series of pyridopyrimidines using this green nanocatalyst.

Result and discussion

The present study followed our continued interest in the development of synthetic strategies to obtain heterocycles of biological importance.[23–27] We investigated the synthesis of 2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitriles through the reaction of 3-(6-amino-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidin-5-yl)-3-oxopropanenitrile **1** and arylaldehydes **2a–j** by using a [γ-Fe_2O_3@HAp-SO_3H] nanocatalyst (Scheme 1). Starting compound **1** was prepared by condensation of



Scheme 1 Synthesis of 2-thioxopyrido[2,3-*d*]pyrimidines **3a–j**.

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thiourea with ethylcyanoacetate in sodium ethoxide,[28] followed by cyanoacetylation of 6-amino-2,3-dihydro-2-thioxo-pyrimidine-4(1*H*)-one with cyanoacetic acid in acetic anhydride.[29]

In initial experiments, to obtain the optimal conditions, the reaction between 3-(6-amino-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3-oxopropanenitrile **1** and 4-chlorobenzaldehyde **2a** in the presence of [γ-Fe_2O_3@HAp-SO_3H] to prepare 7-(4-chlorophenyl)-4,5-dioxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile **3a,** was selected as a model. Different solvents were screened for the synthesis of **3a** and the results are summarised in Table 1. It is evident from the result that DMF at 120 °C is the best solvent (Table 1, entry 4) amongst the solvents selected.

Different catalysts were also compared with [γ-Fe_2O_3@HAp-SO_3H] in the preparation of **3a**. The results showed that the highest yields (96%) and shortest reaction time (1.15 h) are obtained when [γ-Fe_2O_3@HAp-SO_3H] was used as a catalyst in DMF at 120 °C (Table 2).

Under optimal conditions, various arylaldehydes were used to prepare a variety of 2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives **3a–j** in high yields (84–96%) and lower reaction times (1.15–2.5 h) (Table 3). Under present conditions, aliphatic aldehydes such as 3-phenylpropanal produced the desired products (Table 3, entry 3h).

A plausible mechanism for the synthesis of thioxopyrido-[2,3-*d*]pyrimidine-6-carbonitrile derivatives **3a–j** is outlined in Scheme 2. During the reaction, the nanocatalyst [γ-Fe_2O_3@HAp-SO_3H] activates the carbonyl group, facilitates the cyclisation reaction and therefore accelerates the product formation. In this protocol, the rearranged product **4** is not formed (Scheme 3). This was concluded from the treatment of **3** with NaOH 5%, which did not lead to any reaction. The product **4** as a phenolic compound is expected to react with NaOH 5%.

To extend the scope of this method, preparation of 2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-diones **7a–k** by one-pot three-component reaction of 6-amino-2-(alkylthio)pyrimidin-4(3*H*)-one **5**, 1,3-diethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **6** and various arylaldehydes in the presence of nanomagnetic catalyst [γ-Fe_2O_3@HAp-SO_3H] was investigated (Scheme 3).

The reaction conditions were optimised by the synthesis of 5-(4-bromophenyl)-1,3-diethyl-8-(methylthio)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione **7a** as model compound. Therefore, the reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one **5**, 1,3-diethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **6** and bromobenzaldehyde **7a** using nanocatalyst [γ-Fe_2O_3@HAp-SO_3H] was attempted in several solvents such as EtOH, MeOH, AcOH, CH_3CN, H_2O, DMF and THF under reflux conditions. The results showed that EtOH in the presence of [γ-Fe_2O_3@Hap-SO_3H] is the best choice. The catalytic efficiency of nanomagnetic catalyst [γ-Fe_2O_3@HAp-SO_3H] was also compared with various catalysts in the synthesis of **7a** (Table 4). It is evident from the results that [γ-Fe_2O_3@HAp-SO_3H] is the best choice in terms of yield (98%) and reaction time (3 min).

Under optimal conditions, several derivatives of 2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione **7a–k** were synthesised in excellent yields (92–98%) and short reaction times (3–6 min) (Table 5).

Table 1 Solvent effects on the synthesis of 2-thioxopyrido[2,3-*d*] pyrimidine **3a**

Entry	Solvent	Temperature/°C	Time/h	Yield/%[a]
1	EtOH	80	6	40
2	HOAc	100	5	52
3	DMF	100	3	75
4	DMF	120	1.15	96
5	DMF	140	2	85
6	$CHCl_3$	65	8	52

[a]Isolated yield.

Table 2 Synthesis of 2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile **(3a)** in the presence of several catalysts in refluxing DMF at 120 °C

Entry	Catalyst	Amount of catalyst/g $mmol^{-1}$ substrate	Time/h	Yield/%[a]
1	[γ-Fe_2O_3@HAp-SO_3H]	1.0 mol%	1.15	96
2	Piperidine	5 mol%	10	67
3	Et_3N	5 mol%	10	61
4	*p*-TSA	5 mol%	9	78
5	AcOH	10 mol%	12	53
6	NaOEt	10 mol%	12	48

[a]Isolated yield.

Table 3 Synthesis of thioxopyrido[2,3-*d*]pyrimidine-6-carbonitriles **3a–j**

Entry	Ar	Time/h	Yield/%[a]
3a	4-ClC_6H_4	1.15 (5)[b]	96 (60)[b]
3b	4-FC_6H_4	2	96
3c	Thiophen-2-yl	2	87
3d	Pyridin-3-yl	2	84
3e	2-HOC_6H_4	2	84
3f	Naphthalen-2-yl	1.5	85
3g	Pyridin-3-yl	1.75	90
3h	$-CH_2-CH_2-C_6H_5$	1.5	87
3i	[c]	2.5	84
3j	[d]	2.5	86

[a]Isolated yield.
[b]Without catalyst.
[c]R= Cl
[d]R=C_3

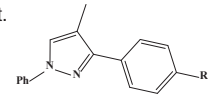


Table 4 Comparison of different catalysts in the synthesis of **7a** in refluxing EtOH

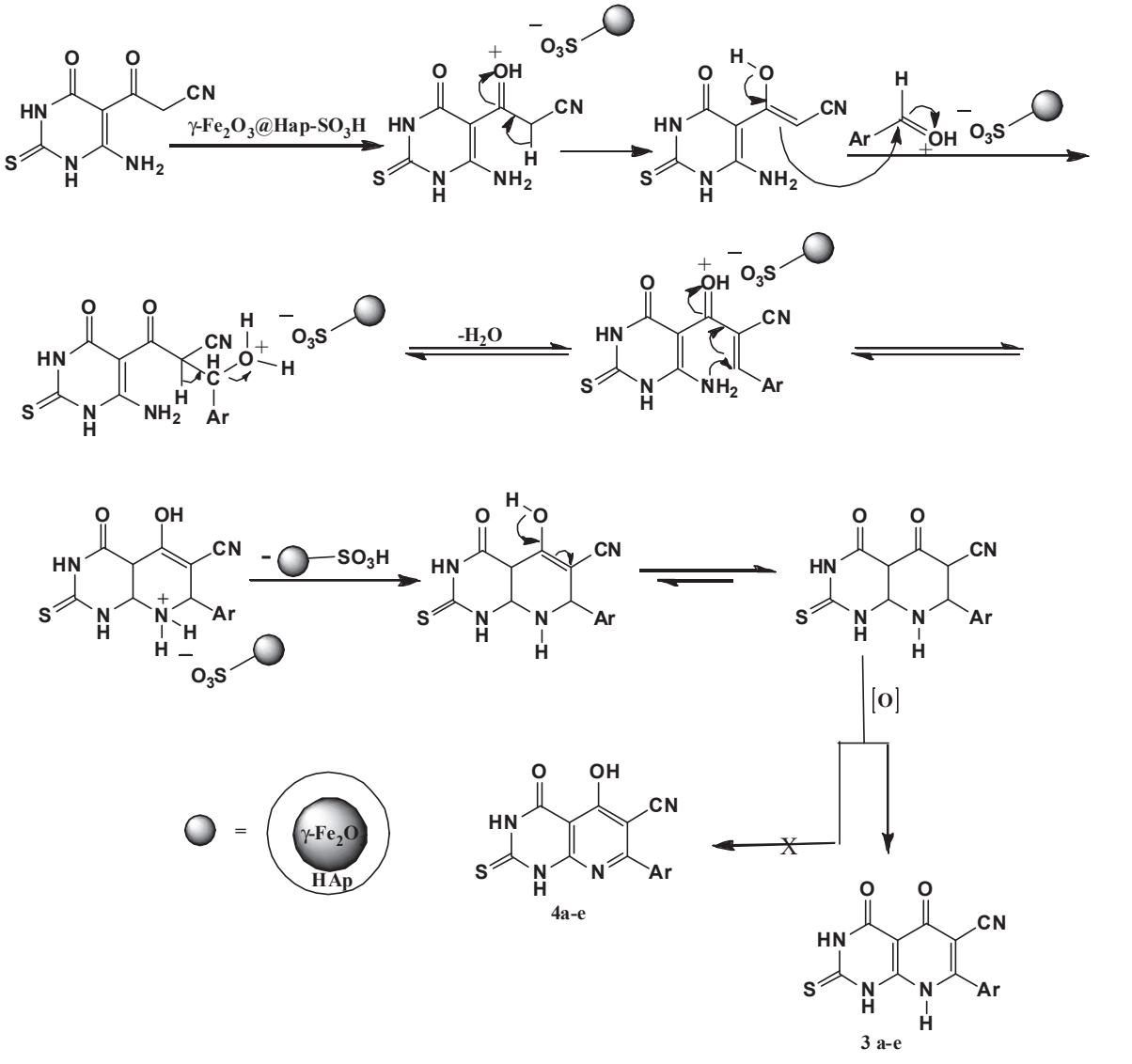
Entry	Catalyst	Amount of catalyst/g $mmol^{-1}$ substrate	Time/min	Yield/%[a]
1	γ-Fe_2O_3@Hap-SO_3H	1.0 mol%	3	98
2	Piperidine	5 mol%	10	88
3	Et_3N	5 mol%	10	84
4	p-TSA	5 mol%	8	78
5	AcOH	10 mol%	8	75
6	NaOEt	10 mol%	9	78

[a]Isolated yield.

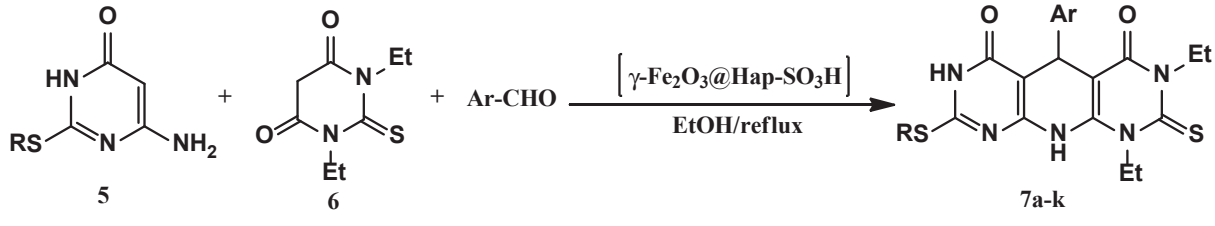
Table 5 Synthesis of 2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*'] dipyrimidine-4,6(1*H*,5*H*)-diones **7a–k**

Entry	Product	Ar	R	Time/min	Yield%[a]
1	**7a**	4-BrC_6H_4	Me	3 (120)[b]	98 (40)[b]
2	**7b**	4-ClC_6H_4	Me	3	98
3	**7c**	3-$NO_2C_6H_4$	Me	5	95
4	**7d**	3-BrC_6H_4	Me	4	94
5	**7e**	2,4-$Cl_2C_6H_3$	Me	3	98
6	**7f**	Naphthalen-1-yl	Me	6	95
7	**7g**	Pyridin-3-yl	Me	4	95
8	**7h**	3-$MeOC_6H_4$	Me	6	93
9	**7i**	4-$O_2NC_6H_4$	Et	4	98
10	**7j**	2,4-diClC_6H_3	Et	3	98
11	**7k**	Naphthalen-1-yl	Et	6	92

[a] Isolated yield.
[b] Without catalyst.



Scheme 2 A plausible mechanism of preparation of 2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitriles **3a–j** in the presence of [γ-Fe_2O_3@HAp-SO_3H].



R = Me, Et

Scheme 3 Synthesis of 2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6 (1*H*,5*H*)-diones **7a–k**.

We also verified the reusability of the nanocatalyst [γ-Fe_2O_3@HAp-SO_3H] in preparation of **3a** and **7a** as model compounds. The catalyst was readily separated from the reaction mixture by using an external magnetic field, washed with ethanol, dried under vacuum and reused in the next run. The results of the reaction in the preparation of **3a** and **7a** as model reaction, revealed that after five successive runs no significant loss of activity is observed.

The structures of all the products were fully characterised by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses.

Experimental

Melting points were measured on an electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DRX-400 in DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts on ^{1}H and ^{13}C NMR were expressed in ppm downfield from tetramethylsilane. Sonication was performed in an Elmasonic S 40H ultrasonic cleaning unit (40 kHz). Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyser and agreed with the calculated values. All the chemicals were purchased from Merck and used

without further purification. All solvents used were dried and distilled according to standard procedures.

Synthesis of **3a–j***: general procedure*

[γ-Fe_2O_3@HAp-SO_3H] was synthesised according to the literature.[18] A mixture of 3-(6-amino-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidin-5-yl)-3-oxopropanenitrile **1** (1 mmol) and an aryl aldehyde **2a–e** (1 mmol) and [γ-Fe_2O_3@HAp-SO_3H] (0.05 g) in DMF (2 mL) was heated at 120 °C. The progress of the reaction was monitored by TLC (EtOAc/petroleum: 3/1). After completion of the reaction, the mixture was cooled, and the catalyst was separated from the reaction mixture by an external magnet. The reaction mixture was diluted with cold water. Pure product was obtained by recrystallisation from EtOH.

Synthesis of **7a–k***: general procedure*

A mixture of 6-amino-2-(alkylthio)pyrimidin-4(3*H*)-one **5** (1 mmol), 1,3-diethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **6** (1 mmol), arylaldehyde (1 mmol) and [γ-Fe_2O_3@HAp-SO_3H] (0.05 g) in EtOH (10 mL) was heated under reflux. The progress of the reaction was monitored by TLC (EtOAc/petroleum: 2/1). After completion of the reaction, the catalyst was separated from the reaction mixture by external magnet and reused in the next run. The reaction mixture was cooled, and the solid obtained was recrystallised from EtOH/H_2O to give the desired pure product.

*7-(4-Chlorophenyl)-4,5-dioxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3a**): Cream powder; m.p. >300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3317, 2190, 1684, 1622, 1587, 1535, 1456, 1508, 1195, 812; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (2H, d, *J*=8.8 Hz, ArH), 7.89 (2H, d, *J*=8.8 Hz, ArH), 13.19 (1H, s, NH), 13.59 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 92.5, 98.5, 115.1, 129.1, 131.1, 135.7, 136.4, 153.8, 163.4, 165.3, 170.8, 176.6 ppm. Anal. calcd for $C_{14}H_7ClN_4O_2S$ (330.75): C, 50.84; H, 2.13; N, 16.94; found: C, 50.71; H, 2.03; N, 16.79%.

*7-(4-Fluorophenyl)-4,5-dioxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3b**): Cream powder; m.p. 233–235 °C; IR (KBr) (ν_{max}/cm^{-1}): 3324, 2231, 1689, 1622, 1548, 1510, 1442, 1163, 806; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45 (2H, t, *J*=9.0 Hz, ArH), 7.49 (2H, dd, *J*=8.8, 5.2 Hz, ArH), 13.09 (1H, s, NH), 13.49 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 92.1, 98.2, 115.1 (d, $^2J_{CF}$=22.0 Hz), 116.1, 131.9 (d, $^3J_{CF}$=8.0 Hz, ArH), 133.3 (d, $^4J_{CF}$=4.0 Hz), 153.7, 163.5, 164.1 (d, $^1J_{CF}$=240.0 Hz), 165.5, 170.6, 176.6 ppm. Anal. calcd for $C_{14}H_7FN_4O_2S$ (314.29): C, 53.50; H, 2.24; N, 17.83; found: C, 53.51; H, 2.21; N, 17.65%.

*4,5-Dioxo-7-(thiophen-2-yl)-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3c**)**:** Brown powder; m.p. 313–314 °C; IR (KBr) (ν_{max}/cm^{-1}): 3431, 2210, 1653, 1585, 1528, 1419, 1122, 811, 713; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (1H, t, *J*=4.4 Hz, ArH), 7.80 (1H, d, *J*=4.8 Hz, ArH), 8.09 (1H, d, *J*=1.6 Hz, ArH), 12.13 (1H, s, NH), 12.61 (1H, s, HN-C=S) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 93.2, 100.6, 116.5, 127.6, 128.9, 131.9, 137.8, 155.3, 157.1, 161.4, 170.0, 175.7 ppm. Anal. calcd for $C_{12}H_6N_4O_2S_2$ (302.34): C, 47.67; H, 2.00; N, 18.53; found: C, 47.45; H, 2.21; N, 18.38%.

*4,5-Dioxo-7-(pyridin-3-yl)-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3d**): Dark orange powder; m.p. 226–228 °C; IR (KBr) (ν_{max}/cm^{-1}): 3452, 2204, 1691, 1626, 1599, 1546, 1506, 1197, 810, 705; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59 (1H, dd, *J*=7.8, 5.0 Hz, ArH), 8.19 (1H, d, *J*=8.0 Hz, ArH), 8.44 (1H, s, HN–C=O), 8.77 (1H, d, *J*=4.0 Hz, ArH), 8.96 (1H, s, ArH),12.50 (1H, s, NH), 12.99 (1H, s, HN–C=S), ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 95.8, 100.3, 117.5, 123.8, 133.9, 136.7, 149.3, 151.1, 155.2, 161.7, 163.3, 173.1, 176.1 ppm. Anal. calcd for $C_{13}H_7N_5O_2S$ (297.29): C, 52.52; H, 2.37; N, 23.56; found: C, 52.44; H, 2.18; N, 23.68%.

*7-(2-Hydroxyphenyl)-4,5-dioxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3e**): Cream powder; m.p. 225–227 °C; IR (KBr) (ν_{max}/cm^{-1}): 3377, 2210, 1660, 1632, 1541, 1504, 1188, 811, 754;. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.11 (1H, m, ArH), 7.25 (1H, d, *J*=8.4 Hz, ArH), 8.33 (1H, t, *J*=7.8 Hz, ArH), 7.56 (1H, d, *J*=8.4 Hz, ArH), 9.87 (1H, s, OH), 12.19 (2H, s, NH), 12.61 (1H, s, HN–C=S) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 99.1, 101.1, 117.4, 118.7, 125.0, 125.9, 128.6, 129.9, 153.6, 155.5, 160.8, 167.5, 174.2, 175.8 ppm. Anal. calcd for $C_{14}H_8N_4O_3S$ (312.28): C, 53.84; H, 2.58; N, 17.94; found: C, 53.69; H, 2.40; N, 17. 81%.

*7-(Naphthalen-2-yl)-4,5-dioxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3f**): Dark orange powder**;** m.p. >300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3348, 3144, 2222, 1684, 1620, 1533, 1458, 1188, 868, 808, 742; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ 7.71–7.63 (2H, m, ArH), 7.94 (1H, dd, *J*=8.4, 1.6 Hz, ArH), 8.05 (1H, d, *J*=8.0 Hz, ArH), 8.10 (1H, d, *J*=7.6 Hz, ArH), 8.13 (1H, d, *J*=8.4 Hz, ArH), 8.48 (1H, s, ArH), 13.60 (1H, s, NH), 13.19 (1H, s, NH) ppm; ^{13}C NMR (100 MHz**,** DMSO-d_6)**:** δ 92.3, 98.2, 115.1, 126.1, 127.7, 128.2, 128.5, 128.7, 129.3, 129.7, 132.5, 134.2, 153.7, 163.8, 166.7, 170.5 176.7 ppm. Anal. calcd for $C_{18}H_{10}N_4O_2S$ (346.36): C, 62.42; H, 2.91; N, 16.18; found: C, 62.38; H, 2.85; N, 16.11%.

*4,5-Dioxo-7-(pyridin-3-yl)-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3g**): Dark orange powder; m.p. >300 °C; IR (KBr) (ν_{max}/cm^{-1})**:** 3439, 2210, 1691, 1626, 1549, 1504, 810, 708; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ 7.62 (1H, dd, *J*=7.8, 4.8 Hz, ArH), 8.23 (1H, d, *J*=8.0 Hz, ArH), 8.76 (1H, d, *J*=4.0 Hz, ArH), 8.99 (1H, s, ArH), 12.72 (2H, br. s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ 94.7, 99.7, 116.5, 124.0, 133.6, 137.1, 149.2, 151.3, 154.7, 162.4, 163.6, 172.1, 176.3 ppm. Anal. calcd for $C_{13}H_7N_5O_2S$ (297.29): C, 52.52; H, 2.37; N, 23.56; found: C, 52.43; H, 2.39; N, 23.45%.

*4,5-Dioxo-7-phenethyl-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3h**): Dark orange powder ; m.p. 250–252 °C; IR (KBr) (ν_{max}/cm^{-1})**:** 3360, 2224, 1666, 1622, 1542, 1446, 1122, 811, 734; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.00 (t, *J*=7.2 Hz, 2H, CH_2), 3.12 (t, *J*=7.6 Hz, 2H, CH_2–Ar), 7.22 (m, 3H, ArH), 7.55 (d, *J*=7.2 Hz, 2H, ArH), 13.03 (2H, br. s, NH) ppm**;** ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.5, 33.9, 98.1, 114.4, 100.4, 126.7, 128.8, 128.9, 153.8, 140.7, 163.5, 169.7, 171.1, 176.5 ppm.

*7-(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dioxo-2-thioxo-1,2,3,4,5,8-hexahydro-4,5-pyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3i**): Cream powder; m.p. >300 °C; IR (KBr) (ν_{max}/cm^{-1})**:** 3390, 2210, 1684, 1635, 1583, 1495, 1118, 850; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37 (1H, m, ArH), 7.46 (2H, d, *J* = 8.9 Hz, ArH), 7.56 (2H, m, ArH), 7.67 (2H, d, *J*=9 Hz, ArH), 7.96 (2H, d, *J*=8.4 Hz, ArH), 8.52 (1H, br. s, NH–C=O), 8.87 (1H, s, =CH–N), 11.84 (1H, s, NH), 12.32 (1H, s, NH–C=O) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 100.6, 101.6, 118.8, 118.9, 120.7, 127.3, 129.0, 129.5, 130.1, 130.2, 132.0, 133.2, 139.5, 149.0, 156.1, 160.4, 162.8, 174.6, 175.7 ppm. Anal. calcd for $C_{23}H_{13}ClN_6O_2S$ (472.91): C, 58.41; H, 2.77; N, 17.77; found: C, 58.22; H, 2.96; N, 17.91%.

*4,5-Dioxo-7-(1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl)-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile* (**3j**): Cream powder; m.p. >300 °C; IR (KBr) (ν_{max}/cm^{-1})**:** 3406, 2220, 1659, 1614, 1587, 1529, 1518, 1140, 814; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (3H, s, CH_3), 7.19 (2H, d, *J*=8 Hz, ArH), 7.39 (1H, m, ArH), 7.48 (2H, d, *J*=8.4 Hz, ArH), 7.58 (ArH, m, 2H,), 7.96 (2H, d, *J*=8 Hz, ArH), 8.92 (1H, s, =CH–N), 12.47 (1H, s, NH), 12.84 (1H, s, NH–C=S) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.3, 99.8, 101.2, 118.9, 119.0, 120.9, 127.2, 127.8, 129.5, 129.9, 130.2, 130.3, 138.0, 139.5, 150.3, 157.1, 163.8, 166.5, 175.4, 177.3 ppm. Anal. calcd for $C_{24}H_{16}N_6O_2S$ (452.49): C, 63.70; H, 3.56; N, 18.57; found: C, 63.51; H, 3.69; N, 18.73%.

*5-(4-Bromophenyl)-1,3-diethyl-8-(methylthio)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7a**): White powder; m.p. 225–227 °C; IR (KBr) (ν_{max}/cm^{-1}): 3450, 3300, 3200, 3060, 2975, 2900, 1620, 1590, 1560, 1430, 1380, 1075, 840; ^{1}HNMR (400 MHz, DMSO-d_6): δ 1.18 (6H, s, 2 $CH_2\underline{CH_3}$), 2.54 (3H, s, SCH_3), 4.45 (4H, br. s, 2 $\underline{CH_2}CH_3$), 5.47 (1H,s, CH), 7.13 (2H, d, *J*=7.6 Hz, ArH), 7.42 (2H, d, *J*=7.6 Hz, ArH), 7.57 (1H, br. s, NH), 13.18 (1H, s, CO–NH) ppm. Anal. calcd for $C_{20}H_{20}BrN_5O_2S_2$ (506.44): C, 47.43; H, 3.98; N, 13.83; found: C, 47.58; H, 3.81; N, 13.65%.

*5-(4-Chlorophenyl)-1,3-diethyl-8-(methylthio)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione*

(**7b**): White powder; m.p. 235–237 °C; IR (KBr) (ν_{max}/cm^{-1}): 3450, 3300, 3200, 3060, 2975, 2900, 1620, 1590,1560,1440, 1380, 1085, 840; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (6H, s, 2CH$_2$CH$_3$), 2.55 (3H, s, SCH$_3$), 4.47 (4H, br. s, 2CH$_2$CH$_3$), 5.51 (1H, s, ArH), 7.13 (2H, d, *J*=8.0 Hz, ArH), 7.30 (2H, d, *J*=8.0 Hz, ArH), 7.59 (1H, br. s, NH), 16.74 (1H, s, CO–NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.5, 12.9, 13.3, 34.3, 43.7, 95.5, 96.1, 128.4, 128.8, 128.8, 128.9,130.0, 130.8, 138.2, 160.6, 161.2, 164.3, 174.8 ppm. Anal. calcd for $C_{20}H_{20}ClN_5O_2S_2$ (461.99): C, 52.00; H, 4.36; N, 15.16; found: C, 52.15; H, 4.48; N, 15.01%.

*1,3-Diethyl-8-(methylthio)-5-(3-nitrophenyl)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7c**): White powder; m.p. 233–235 °C; IR (KBr) (ν_{max}/cm^{-1}): 3460, 3350, 3200 ,3100, 2990, 2900,1615, 1580, 1560, 1430, 1380, 1520,1340, 850, 780, 685; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (6H, s, 2CH$_2$CH$_3$), 2.57 (3H, s, SCH$_3$), 4.49 (4H, m, 2CH$_2$CH$_3$), 5.65 (1H, s, CH), 7.50–7.64 (3H, m, ArH), 7.88 (1H, s, NH), 8.08 (1H, d, *J*=6.4 Hz, ArH), 16.72 (1H, br. s, CO–NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6, 13.3, 34.7, 43.7, 95.0, 95.6, 121.5, 121.6, 129.9, 130.1, 134.3, 141.8, 148.3, 160.9, 164.3, 174.9 ppm. Anal. calcd for $C_{20}H_{20}N_6O_4S_2$ (472.54): C, 50.83; H, 4.27; N, 17.78; found: C, 50.61; H, 4.13; N, 17.54%.

*5-(3-Bromophenyl)-1,3-diethyl-8-(methylthio)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7d**): White powder; m.p. 223–225 °C; IR (KBr) (ν_{max}/cm^{-1}): 3495, 3350, 3200, 3050, 2960, 2900, 2850, 1620, 1610, 1565, 1460, 1380, 1100, 870, 780, 680; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (6H, s, 2CH$_2$CH$_3$), 2.56 (3H, s, SCH$_3$), 4.47 (4H, br. s, 2CH$_2$CH$_3$), 5.55 (1H, s, CH), 7.10–7.38 (4H, m, ArH), 7.59 (1H, br. s, NH), 16.75 (1H, br. s, NH–CO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6):δ 12.6, 12.7, 13.3, 34.5, 43.7, 95.3, 95.9, 122.1, 126.2, 129.2, 129.6, 130.7, 142.1, 160.7, 163.1, 164.0, 164.3, 174.8 ppm. Anal. calcd for $C_{20}H_{20}BrN_5O_2S_2$ (506.44): C, 47.43; H, 3.98; N, 13.83; found: C, 47.31; H, 3.79; N, 13.68%.

*5-(2,4-Dichlorophenyl)-1,3-diethyl-8-(methylthio)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7e**): White powder; m.p. 228–30 °C; IR (KBr) (ν_{max}/cm^{-1}): 3400, 3300, 3200, 3050, 2960, 2900, 2860, 1635, 1610, 1580, 1520, 1460, 1380, 1100, 1080, 860, 780, 760; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (6H, t, *J*=6.8 Hz, 2CH$_2$CH$_3$), 2.54 (3H, s, SCH$_3$), 4.47 (4H, q, *J*=6.8 Hz, CH$_2$CH$_3$), 5.50 (1H, s, CH), 7.34 (2H, m, ArH), 7.50 (1H, s, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6, 12.9, 13.3, 34.0, 43.3, 43.7, 95.0, 95.6, 127.1, 129.7, 131.5, 131.7, 132.1, 134.0, 136.6, 160.5, 161.3, 163.2, 163.8, 174.8 ppm. Anal. calcd for $C_{20}H_{19}Cl_2N_5O_2S_2$ (496.43): C, 48.39; H, 3.86; N, 14.11; found: C, 48.55; H, 3.70; N, 14.39%.

*1,3-Diethyl-8-(methylthio)-5-(naphthalene-1-yl)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7f**): White powder; m.p. 233–235 °C; IR (KBr) (ν_{max}/cm^{-1}): 3500, 3300, 3200, 3050, 2980, 2900, 2850, 1610, 1580, 1440, 1380, 860, 795, 775, 740; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (6H, m, 2CH$_2$CH$_3$), 2.56 (3H, s, SCH$_3$), 4.51 (4H, m, 2CH$_2$CH$_3$), 6.08 (1H, s, CH), 7.38 (4H, m, ArH), 7.62 (1H, d, *J*=8.4 Hz, ArH), 7.79 (1H, d, *J*=8.0 Hz, ArH), 7.90 (1H, d, *J*=7.6 Hz, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6):δ 12.4, 12.7, 13.3, 33.4, 43.6, 81.4, 97.3, 124.0, 125.5, 125.6, 126.0, 127.6, 129.2, 131.5, 132.0, 134.3, 135.0, 160.3, 161.7, 162.6, 163.0, 164.7, 174.6 ppm. Anal. calcd for $C_{24}H_{23}N_5O_2S_2$ (477.6): C, 60.36; H, 4.85; N, 14.66; found: C, 60.21; H, 4.59; N, 14.79%.

*1,3-Diethyl-8-(methylthio)-5-(pyridine-3-yl)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7g**): White powder; m.p. 226–228 °C; IR (KBr) (ν_{max}/cm^{-1}): 3500, 3400, 3300, 3060, 2970, 2900, 1620, 1585, 1560, 780, 680; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (6H, t, *J*=6.8 Hz, 2CH$_2$CH$_3$), 2.46 (3H, s, SCH$_3$), 4.42 (4H, m, 2CH$_2$CH$_3$), 5.86 (1H, s, CH), 7.09 (1H, br. s, NH), 7.76 (1H, dd, *J*=7.6, 5.6 Hz, ArH), 7.99 (1H, d, *J*=8.0 Hz, ArH), 8.40 (s, 1H, ArH), 8.59 (1H, d, *J*=5.2 Hz, ArH) ppm. Anal. calcd for $C_{19}H_{20}N_6O_2S_2$ (428.53): C, 53.25; H, 4.70; N, 19.61; found: C, 53.11; H, 4.91; N, 19.45%.

*1,3-Diethyl-8-(methylthio)-5-(3-methoxyphenyl)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7h**): White powder; m.p. 225–227 °C; IR (KBr) (ν_{max}/cm^{-1}) (KBr): 3400, 3300, 3200, 3066, 2960, 2900, 1620, 1560, 1480, 1450, 1370, 1260, 1040, 870, 780, 700; ^{1}H NMR (400 MHz, DMSO-d_6):δ 1.20 (6H, br. s, 2CH$_2$CH$_3$), 2.56 (3H, s, SCH$_3$), 3.69 (3H, s, OCH$_3$), 4.48 (4H, br. s, CH$_2$CH$_3$), 5.50 (1H, s, CH), 6.61 (1H, s, ArH), 6.68 (1H, d, *J*=7.6 Hz, ArH), 6.77 (1H, dd, *J*=8.4 Hz, 2.4 Hz, ArH),7.19 (1H, t, *J*=7.6 Hz, ArH), 7.55 (1H, br. s, NH), 16.81 (1H, br. s, NH–CO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.5, 12.9, 13.3, 34.6, 41.4, 43.7, 56.5, 95.5, 96.5, 111.0, 113.2, 119.2, 129.6, 159.6, 159.7, 160.5, 161.6, 162.0, 164.0, 164.3, 174.7 ppm. Anal. calcd for $C_{21}H_{23}N_5O_3S_2$ (457.57): C, 55.12; H, 5.07; N, 15.31; found: C, 55.01; H, 5.18; N, 15.12%.

*1,3-Diethyl-8-(ethylthio)-5-(4-nitrophenyl)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7i**): White powder; m.p. 230–232 °C; IR (KBr) (ν_{max}/cm^{-1}): 3420, 3300, 3200, 3050, 2990, 2910, 1620, 1560, 1500, 1440, 1380, 1500, 1340, 840; ^{1}H NMR (400 MHz, DMSO-d_6):δ 1.20 (6H, t, *J*=6.4 Hz, 2CH$_2$CH$_3$), 1.35 (3H, t, *J* = 7.2 Hz, SCH$_2$CH$_3$), 3.19 (2H, m, SCH$_2$CH$_3$), 4.47 (4H, q, *J*=6.4 Hz, 2CH$_2$CH$_3$), 5.64 (1H, s, CH), 7.42 (2H, d, *J*=8.4 Hz, ArH), 7.63 (1H, br. s, NH), 8.13 (2H, d, *J*=8.4 Hz, ArH), 16.67 (1H, s, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6):δ 12.6, 15.0, 24.9, 35.1, 43.7, 95.3, 95.7, 123.7, 128.5, 146.2, 148.0, 160.3, 161.8, 163.9, 164.0, 164.4, 174.9 ppm. Anal. calcd for $C_{21}H_{22}N_6O_4S_2$ (486.57): C, 51.84; H, 4.56; N, 17.27; found: C, 51.60; H, 4.32; N, 17.02%.

*5-(2,4-Dichlorophenyl)-1,3-diethyl-8-(ethylthio)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7j**): White powder; m.p. 226–228 °C; IR (KBr) (ν_{max}/cm^{-1}): 3400, 3300, 3200, 3060, 2970, 2900, 2860, 1640,1610, 1580, 1520, 1460, 1380, 1100, 1080, 850, 780, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (6H, t, *J*=6.8 Hz, 2CH$_2$CH$_3$), 1.31 (3H, t, *J*=7.2 Hz, SCH$_2$CH$_3$), 3.14 (2H, m, SCH$_2$CH$_3$), 4.45 (4H, q, *J*=6.8 Hz, 2CH$_2$CH$_3$), 5.52 (1H, s, CH), 7.34 (2H, m, ArH), 7.37 (1H, br. s, NH), 7.45 (1H, s, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.3, 12.6, 15.1, 24.8, 34.0, 43.3, 43.6, 95.4, 95.9, 127.1, 129.7, 131.5, 131.7, 132.0, 134.0, 159.9, 161.3, 163.5, 164.0, 164.1, 174.7 ppm. Anal. calcd for $C_{21}H_{21}Cl_2N_5O_2S_2$ (510.46): C, 49.41; H, 4.15; N, 13.72; found: C, 49.18; H, 4.09; N, 13.55%.

*1,3-Diethyl-8-(ethylthio)-5-(naphthalen-1-yl)-2-thioxo-2,3,7,10-tetrahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,5*H*)-dione* (**7k**): White powder; m.p. 232–234 °C; IR (KBr) (ν_{max}/cm^{-1}): 3495, 3300, 3200, 3059, 2960, 2910, 2854, 1615, 1580, 1440, 1380, 860, 790, 775, 740; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (6H, m, 2CH$_2$CH$_3$), 1.33 (3H, t, *J*=7.2 Hz, SCH$_2$CH$_3$), 3.16 (2H, m, SCH$_2$CH$_3$), 4.45 (4H, m, 2CH$_2$CH$_3$), 6.08 (1H, s, CH), 7.34–7.46 (4H, m, ArH),7.62 (1H, d, *J*=8.4 Hz, ArH), 7.79 (1H, d, *J* =8.0 Hz, ArH), 7.90 (1H, d, *J*=7.6 Hz, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.5, 12.8, 15.0, 24.8, 33.4, 43.5, 43.7, 81.6, 97.4, 124.0, 125.4, 125.5, 125.7, 125.9, 127.6, 129.2, 131.5, 134.3, 152.1, 159.7, 161.6, 161.8, 164.7, 174.6 ppm. Anal. calcd for $C_{25}H_{25}N_5O_2S_2$ (491.63): C, 61.08; H, 5.13; N, 14.25; found: C, 61.29; H, 5.01; N, 14.14%.

Conclusions

In summary, we have demonstrated an eco-friendly, efficient and versatile approach for the synthesis of novel pyridopyrimidines **3a–j** and **7a–k** using [γ-Fe$_2$O$_3$@HAp-SO$_3$H] as a supported magnetic nanocatalyst. Reusability of the catalyst, short reaction times, easy work-up of the products, excellent yields and mild reaction conditions are the notable features of this protocol.

Electronic Supplementary Information

The ESI (NMR spectra of **3a**) is available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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