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One-Pot Synthesis of Novel Derivatives of Dithioxopyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6-diones Using Hap-Encapsulated γ-Fe_2O_3 Supported Sulfonic Acid Nanocatalyst

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Abstract. A series of novel dithioxopyrido[2,3-*d*:6,5-*d*]dipyrimidine-4,6-dione derivatives were synthesized through a one-pot three-component approach using HAp-encapsulated-γ-Fe_2O_3[γ-Fe_2O_3@HAP-SO_3H] catalyzed condensation of 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one and various substituted aryl aldehydes at 110 °C in DMF. In this protocol the use of nanocatalyst provided a green, useful and rapid method to generate the products in short reaction times and good to excellent yields (70–95%) and the catalyst is easily separated by applying an external magnetic field.

Keywords: Pyrido[2,3-*d*]pyrimidines, three-component, dipyrimidine, [γ-Fe_2O_3@HAP-SO_3H], nanocatalyst.

1. Introduction

Nanometer-sized materials have attracted substantial interest in the scientific community because of their special properties. The relatively large surface area and highly active surface sites of nanoparticles enable them to have a wide range of potential applications. Magnetic iron oxide nanoparticles (MNPs) as a new kind of nanometer-sized material, have multiple practical applications, such as chemistry, physics, medicine, and biology due to their multifunctional properties such as small size, superparamagnetism, high reactivity, low toxicity and high thermal and mechanical stability [1-4]. Additionally, the magnetic properties make the recovery of the catalyst easy by mean of an external magnetic field [5,6]. Recent studies show that magnetic nanoparticles are excellent catalysts for organic reactions [7-8].

MNPs as solid acid catalysts have acquired organic chemists' attention as a new alternative to porous materials for supporting catalytic transformations. Due to their unique properties, magnetic nanoparticles have found potential applications in various fields, such as magnetically assisted drug delivery, magnetic resonance imaging (MRI) contrast agents, hyperthermia and magnetic separation of biomolecules. However, for many applications it is crucial to develop protection strategies to chemically stabilize the naked magnetic nanoparticles, thus, in the fabrication of core–shell magnetic particles, hydroxyapatite has received considerable attention as one of the most ideal biocompatible materials for encapsulated iron oxide NPs. On the other hand, the development of new solid acids is expected to have a major impact on industrial applications as well as for basic research. This problem could be overcome by designing different Brønsted acids (SO_3H, $HClO_4$, HBF_4) on γ-Fe_2O_3@SiO_2 [9,10] and functionalized hydroxyapatite-encapsulated γ-Fe_2O_3 magnetic nanoparticles [11-14].

In addition, pyrimidine and its fused heterocyclic systems are significant among various heterocycles, as they are found to possess valuable pharmaceutical and biological properties [15]. In particular, the synthesis of pyridopyrimidine and their derivatives remains of great interest in organic chemistry, because some of them exhibit significant biological and pharmacological activities, such as antifolate

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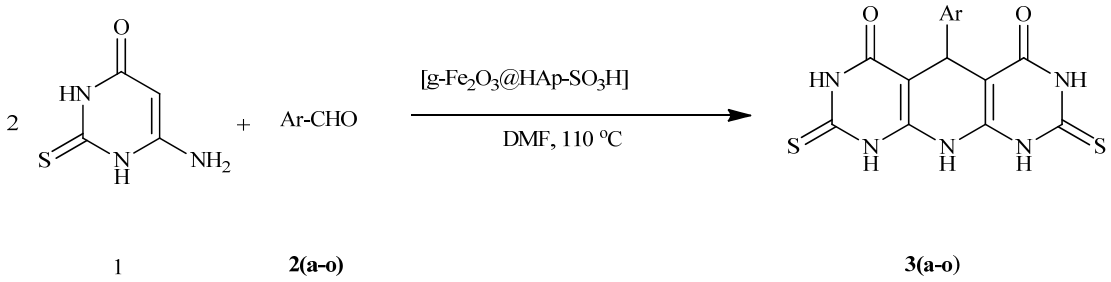
activity [16], antibacterial activity [17], tyrosine kinase activity [18], antimicrobial activity [19], calcium channel antagonists activity [20], anti-inflammatory and analgesic activity [21], antileishmanial activity [22], tuber-culostatic activity [23], anticonvulsants activity [24], diuretic and potassium-sparing activity [25], antiaggressive activity [26], and antitumor activity [27].

Several approaches have been developed for the synthesis of pyridopyrimidines [28,29], such as the reaction of benzylidene derivatives of malononitrile with 6-amino-3,4-dihydropyrimidine in refluxing ethanol [30,31]; the reaction of 6-amino-1-thio uracil with ethyl-3-phenyl-2- cyanoacrylate in absolute ethanol and in the presence of Et_3N by heating [32,33]; the three-component reaction of aldehydes, alkyl nitriles and aminopyrimidines in water and in the presence of KF-Al_2O_3 as catalyst [34]; the three-component reaction catalyzed by triethyl benzyl ammonium chloride (TEBAC) [35] or reaction of amino-uracil with α,β-unsaturated compounds in ionic liquid at 90 °C [36]. Some of the reported methods suffer from disadvantages such as multi-step synthesis with the use of expensive harmful reagents, low yields and longer reaction times. Thus, the development of efficient method for the synthesis of biologically active compounds such as pyridopyrimidines, in one-step would be highly valuable and desirable.

In continuation of our interst for the development of environmentally friendly procedures and sustainable methods for the synthesis of biologically important compounds [37-40], herein we wish to report our novel method for the one-pot three-component synthesis of dithioxopyrido [2,3-d:6,5-d']dipyrimidine-4,6-diones using [γ-Fe_2O_3@HAp-SO_3H] as a recyclable nanocatalyst.

2. Results and Discussion

As a starting point, the requisite starting material 1 (Scheme 1) was prepared by condensation of thiourea with ethyl cyanoacetate in sodium ethoxide according to the known procedures [41]. Nanocatalyst (γ-Fe_2O_3@HAP-SO_3H) was synthesized according to the previously reported procedure [11].



Ar = 2-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 4-FC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4,3-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-MeC_6H_4, 3-$MeOC_6H_4$, C_6H_5,1-Naphthyl, 2-ClC_6H_4, 2-HOC_6H_4

Scheme 1. Synthesis of dithioxopyrido [2,3-*d*:6,5-*d*]dipyrimidine-4,6-dione derivatives (**3a-o**).

To optimize the desired reaction conditions, the three-component reaction of 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1H)-one 1, (2 mmol) 2-nitrobenzaldehyde 2a (1 mmol), and γ-Fe_2O_3@HAP-SO_3H was used as a model system. The reaction mixture was heated at 110 oC in DMF, which produced the product 3a in 20 min and 85% yield.

To explore the scope and versatility of this method and the effect of various parameters, preparation of 3a as a model reaction was attempted in various solvents such as DMF, EtOH, THF, ethylene glycol, CH_3Cl and H_2O were investigated. The results are summarized in Table 1. It is clear from the results that the reaction in DMF produced the product in lower reaction time and higher yield (85%).

Table 1. Screening of different solvent for the synthesis of **3a** in the presence of γ-Fe_2O_3@HAP-SO_3H.

Entry	Solvent	Temperature (°C)	Time (min)	Yields (%)a

1	DMF	110	20	85
2	EtOH	80	24	60
3	THF	65	28	55
4	ethylene glycol	110	18	65
5	$CHCl_3$	60	32	50
6	H_2O	100	35	-

[a] Isolated yield

More over in order to compare the catalytic activity of γ-Fe_2O_3@HAP-SO_3H with other catalysts in preparation of 3a, catalytic activity of various acidic and basic catalysts were evaluated for the model reaction in DMF at 110 °C. The results are summarized in Table 2. It is evident from Table 2, that γ-Fe_2O_3@HAP-SO_3H successfully promotes this coupling reaction and gives the best result (entry 6). We also verified the amount of the catalyst in preparation of 3a and the best result was obtained using 0.01 g γ-Fe_2O_3@HAP-SO_3H at 110 °C in DMF.

Table 2. Comparison of efficiency of various catalysts in one-pot synthesis of **3a** in DMF at 110 °C.

Entry	Catalyst [a]	Time (min.)	Yields (%)
1	*P*-TSA	250	55
2	AcOH	300	70
3	Et_3N	350	45
4	*L*-Proline	320	50
5	DABCO	370	40
6	γ-Fe_2O_3@HAP-SO_3H	20	85
7	γ-Fe_2O_3@HAP-SO_3H	45	70
8	γ-Fe_2O_3@HAP-SO_3H	45	75

[a]Amount of catalyst used for entries 1-6 (0.01 g/mmol substrate), 7 (0.005 g/mmol substrate), 8 (0.02 g/mmol substrate).

Using the optimized conditions, several dithioxopyrido [2,3-d:6,5-d']dipyrimidine-4,6-diones derivatives were synthesized (Scheme 1). The results are summarized in Table 3. The structure of all products was established by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses.

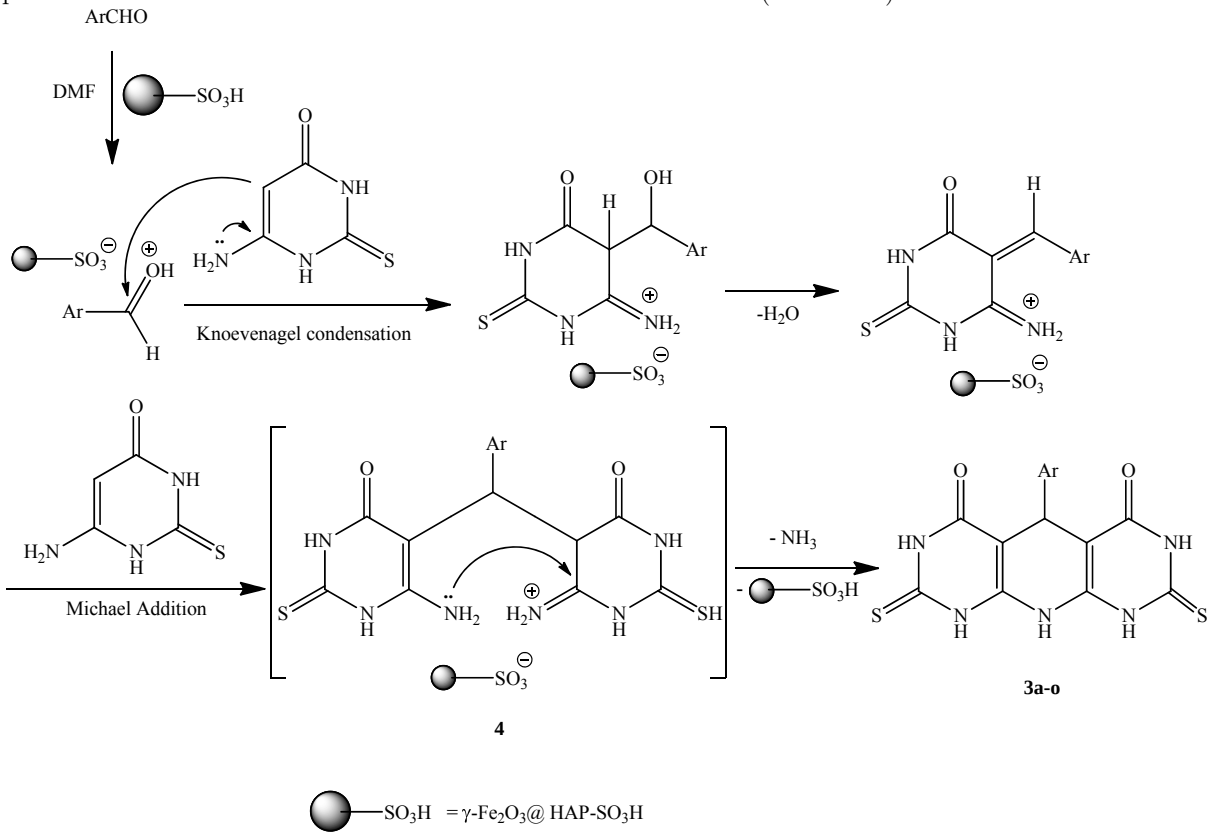
Table 3. One-pot synthesis of dithioxopyrido [2,3-d:6,5-d']dipyrimidine-4,6-diones derivatives (3a–o) in the presence γ-Fe_2O_3@HAP-SO_3H as nanocatalyst at 110 °C.

Entry	Ar	Mp (°C)	Classical		γ-Fe_2O_3@HAP-SO_3H	
			Time (h)	Yields (%)[a]	Time (min)	Yields (%)[a,b]
3a	2-$NO_2C_6H_4$	>300	5	70	20	85
3b	2,4-$Cl_2C_6H_3$	>300	3	82	25	90
3c	4-FC_6H_4	>300	3	80	27	90
3d	4-BrC_6H_4	>300	3	78	30	90
3e	3-BrC_6H_4	>300	4	75	33	87
3f	3-$NO_2C_6H_4$	>300	4	72	35	85
3g	4-ClC_6H_4	>300	3	85	40	95
3h	4-$MeOC_6H_4$	>300	3	65	45	82
3i	3,4-$(MeO)_2C_6H_3$	>300	4	62	45	78
3j	4-MeC_6H_4	>300	6	60	50	75
3k	3-$MeOC_6H_4$	>300	5	57	53	72
3l	Ph	>300	5	55	55	70
3m	1-Naphthyl	>300	4	50	60	73
3n	2-ClC_6H_4	>300	5	42	60	75
3o	2-HOC_6H_4	>300	6	40	75	70

[a] Isolated yields, [b] Identified by spectroscopic analysis (IR, ^{1}H NMR, ^{13}C NMR).

Since, catalyst reusability is very important from both economic and environmental points of view, the catalytic reusability of γ-Fe_2O_3@HAP-SO_3H was investigated in several subsequent runs. The nanocatalyst was separated from the reaction medium simply by an external magnetic field, washed with ethanol, dried under vacuum and reused for the subsequent reactions. After 10 successive runs the catalytic activity of γ-Fe_2O_3@HAP-SO_3H was almost remained unchanged. The high reusability of the catalyst can be explained by its high thermal and mechanical stability and vast surface area owing to an extremely high porosity.

The mechanism of this multicomponent reaction involves a Knoevenagel condensation/Michael addition cascade process. To form the reaction product, intermediates 4 are attacked by exocyclic NH_2-group followed by the release of NH_3 and catalyst. The use of γ-Fe_2O_3@HAP-SO3H nanocatalyst provides efficient acidic sites and therefore facilitates the reaction (Scheme. 2).



Scheme 2: A plausible mechanism for the synthesis of dithioxopyrido [2,3-*d*:6,5-*d*]dipyrimidine-4,6-dione **3** using γ-Fe_2O_3@HAP-SO_3H.

3. Conclusion

In summary, for the first time we showed that [γ-Fe_2O_3@HAp]supported sulfonic acid was an effective heterogeneous catalyst for the one-pot synthesis of dithioxopyrido [2,3-d:6,5-d']dipyrimidine-4,6-dione derivatives 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1H)-one from various substituted aryl aldehydes at 110 °C in DMF. The mild reaction conditions, cost-effective catalyst, high yields, easy work-up procedures, make it a useful alternative to previously applied procedures. Compared with nonmagnetic nanoparticle catalytic systems, the present protocol combines the advantages of solid Brønsted acid and magnetic nanoparticles and offers great potentials for the rapid synthesis of pyrido [2,3-d]pyrimidines.

4. Experimental

4.1 Material and Methods

Melting points were measured on an Electro thermal 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 using TMS as an internal standard. Elemental analyses were performed on a Carlo-Erba EA1110CNNO-S analyzer and agreed (within 0.30) with the calculated values. XRD was carried out on a Philips X-Pert MPD diffractometer using Co tube. Scanning electron microphotographs (SEM) were obtained on a PHILIPS XL30 electron microscope. All the chemicals were purchased from Merck and used without further purification. All solvents used were dried and distilled according to standard procedures.

4.2 General Procedure for Preparation of Dithioxopyrido [2,3-d:6,5-d']dipyrimidine-4,6-diones

To a mixture of 6-amino-2, 3-dihydro-2-thioxopyrimidin-4(1H)-one 1 (2 mmol) and aryl aldehyde 2 (1 mmol) in DMF (5 mL) was added γ -Fe_2O_3@HAP-SO3H (10 mg, 0.09 mmol%) and the reaction mixture was stirred mechanically at 110 °C. After the completion of the reaction, which was monitored by TLC analysis, the reaction mixture was diluted with hot ethanol and the catalyst was easily separated from the reaction mixture by an external magnet. The product obtained was collected by filteration, washed with ethanol and recrystallized from appropriate solvent to furnish the desired pure product (3a–o). Some data of selected compounds are listed below.

4.2.1 2,8-Dithioxopyrido-5-(2-nitrophenyl)-5,10-dihydropyrido[2,3-d:5,6-d']-dipyrimidine-4,6(3H,7H)-dione (3a)

Yield 85%: white powder; Mp >300 °C; IR (KBr, cm-1): 3401 (N-H), 3064, 2898, 1632 (CONH), 1551, 1456, 1551, 1355 (NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.11 (brs, 2H, NH), 11.93 (brs, 2H, NH), 7.66 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.56 (t, 1H, J = 7.2 Hz, H_{Ar}), 7.42 (t, 1H, J = 7.8 Hz, H_{Ar}), 7.35 (d, 1H, J = 8.0 Hz, H_{Ar}), 6.64 (brs, 1H, NH), 5.88 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 175.0, 173.3 (C=S), 163.5, 163.1 (C=O), 153.9, 149.9, 132.6, 132.4, 129.0, 127.6, 124.3, 121.9, 90.2, 89.0, 39.3. Anal. Calculated for C15H10N6O4S2 (402.41), Found: C, 44.65; H, 2.35; N, 20.72 requires C, 44.77; H, 2.50; N, 20.88%.

4.2.2 2,8-Dithioxopyrido-5-(2,4-dichlorophenyl)-5,10-dihydropyrido[2,3-d:5,6-d'] dipyrimidine-4,6(3H,7H)-dione (3b)

Yield: 90%; White powder; Mp >300 °C; IR (KBr, cm^{-1}): 3390, 3152 (N-H), 1651 (CONH), 1549, 1164 (C=S), 1046 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.10 (brs, 2H, NH), 11.95 (brs, 2H, NH), 7.47 (d, 1H, J = 2.4 Hz, H_{Ar}), 7.34 (dd, 1H, J = 8.4, 2.4 Hz, H_{Ar}), 7.28 (d, 1H, J = 8.4 Hz, H_{Ar}), 6.57 (brs, 1H, NH), 5.27 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.2, 173.1 (C=S), 163.1, 163.0 (C=O), 153.5, 153.4, 133.6, 131.6, 130.8, 129.3, 128.8, 127.2, 90.2, 89.8, 32.1. Anal. Calculated for $C_{15}H_9C_{l2}N_5O_2S_2$ (426.30), Found: C, 42.50; H, 2.01; N, 16.32 requires C, 42.26; H, 2.13; N, 16.43%.

4.2.3 2,8-Dithioxopyrido-5-(4-flouorophenyl)-5,10-dihydropyrido[2,3-d:5,6-d'] dipyrimidine-4,6(3H,7H)-dione (3c)

Yield 90%: white powder; Mp >300 °C; IR (KBr, cm^{-1}): 3393, 3163 (N-H), 2961, 1608 (CONH), 1279 (C-N), 1218 (C-F), 1169 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.06 (brs, 2H, NH), 11.85 (brs, 2H, NH), 7.10-6.98 (m, 4H, H_{Ar}), 6.76(brs, 1H, NH), 5.30 (s, 1H, CH), ^{13}C NMR (100 MHz, DMSO-d6): δ(ppm) = 172.7, 172.0 (C=S), 162.9, 161.9 (C=O), 158.7, 153.3, 133.8, 128.4, 128.3, 114.5, 90.1, 31.9. Anal. Calculated for $C_{15}H_{10}FN_5O_2S_2$ (375.40), found: C, 47.84; H, 2.53; N, 18.42 requires C, 47.99; H, 2.68; N, 18.66%.

4.2.4 2,8-Dithioxopyrido-5-(4-bromophenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3d)

Yield 90%: white powder; Mp >300 °C; (KBr, cm^{-1}): 3333, 3147 (N-H), 1603 (CONH), 1541, 1233 (C-N), 1172 (C=S), 1065 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.12 (brs, 2H, NH), 11.88 (brs, 2H, NH), 7.42 (d, 2H, J = 8.2 Hz, H_{Ar}), 7.06 (d, 2H, J = 8.2 Hz, H_{Ar}), 6.79 (brs, 1H, NH), 5.30 (brs, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.2, 172.5 (C=S), 163.4, 162.8 (C=O), 153.9, 153.5, 138.0, 131.1, 129.5, 124.8, 124.6, 123.2, 90.3, 89.0, 36.3. Anal. Calculated for $C_{15}H_{10}BrN_5O_2S_2$ (436.94), Found: C, 41.14; H, 2.15; N, 16.12 requires C, 41.29; H, 2.31; N, 16.05%.

4.2.5 2,8-Dithioxopyrido-5-(3-bromophenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3e)

Yield 87%: white powder; Mp >300 °C; (KBr, cm^{-1}): 3401, 3161 (N-H), 3036, 1609 (CONH), 1551, 1279 (C-N), 1178 (C=S), 1041 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.13 (brs, 2H, NH), 12.00 (brs, 2H, NH), 7.34 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.23-7.19 (m, 2H, H_{Ar}), 7.11 (d, 1H, J = 8.0 Hz, H_{Ar}), 6.79 (brs, 1H, NH), 5.36 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.3, 173.2 (C=S), 163.4, 162.8 (C=O), 154.9, 153.9, 141.6, 130.5, 129.7, 128.8, 126.2, 121.9, 90.2, 78.7, 36.3. Anal. Calculated for $C_{15}H_{10}BrN_5O_2S_2$ (436.94), Found: C, 41.42; H, 2.13; N, 15.51 requires C, 41.29; H, 2.31; N, 16.05%.

4.2.6 2,8-Dithioxopyrido-5-(3-nitrophenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3f)

Yield 85%: White powder; Mp >300 °C; (KBr, cm^{-1}): 3398, 3158 (N-H), 2962, 1699 (CONH), 1547, 1349 (NO_2), 1206 (C-N), 1174 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.18 (brs, 2H, NH), 11.96 (brs, 2H, NH), 8.05 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.86 (brs, 1H, H_{Ar}), 7.61- 7.53 (m, 2H, H_{Ar}), 6.81 (brs, 1H, NH), 5.45 (brs, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.4, 172.5 (C=S), 163.5, 161.5 (C=O), 154.0, 148.3, 141.3, 134.3, 129.9, 121.7, 121.1, 119.3, 91.0, 89.8, 33.0. Anal. Calculated for $C_{15}H_{10}N_6O_4S_2$ (402.41), Found: C, 44.55; H, 2.26; N, 20.68 requires C, 44.77; H, 2.50; N, 20.88%.

4.2.7 2,8-Dithioxopyrido-5-(4-chlorophenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3g)

Yield 95%: white powder; Mp >300 °C; (KBr, cm^{-1}): 3338, 3147 (N-H), 1605 (CONH), 1543, 1233 (C-N), 1172 (C=S), 1092 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d6): δ(ppm) = 12.12 (brs, 2H, NH), 11.89 (brs, 2H, NH), 7.28 (d, 2H, J = 8.2 Hz, H_{Ar}), 7.11 (d, 2H, J = 8.0 Hz, H_{Ar}), 6.79 (brs, 1H, NH), 5.32 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.3, 173.1 (C=S), 163.4, 162.8 (C=O), 154.9, 153.9, 137.3, 130.4, 129.0, 128.2, 126.2, 121.9, 90.4, 89.8, 32.5. Anal. Calculated for $C_{15}H_{10}ClN_5O_2S_2$ (391.86), Found: C, 45.74; H, 2.43; N, 17.58 requires C, 45.98; H, 2.57; N, 17.87%.

4.2.8 2,8-Dithioxopyrido-5-(4-methoxyphenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3h)

Yield 82%: white powder; Mp >300 °C; (KBr, cm^{-1}): 3379, 3131 (N-H), 2958, 1612 (CONH), 1455, 1235 (C-N), 1170 (C=S), 1041 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.07 (brs, 2H, NH), 11.85 (brs, 2H, NH), 6.99 (d, 2H, J = 8.0 Hz, H_{Ar}), 6.81 (d, 2H, J = 8.0 Hz, H_{Ar}), 6.60 (brs, 1H, NH), 5.30 (s, 1H, CH), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.2, 173.1 (C=S), 163.5, 162.3 (C=O), 157.6, 153.8, 141.6, 129.9, 128.0, 126.2, 121.9, 113.7, 91.0, 78.7, 55.4, 32.2. Anal. Calculated for $C_{16}H_{13}N_5O_3S_2$ (387.44), Found: C, 49.44; H, 3.23; N, 18.01 requires C, 49.60; H, 3.38; N, 18.08%.

4.2.9 2,8-Dithioxopyrido-5-(3,4-dimethoxyphenyl)-5,10-dihydropyrido[2,3-d:5,6-d'] dipyrimidine-4,6(3H,7H)-dione (3i)

Yield 78%: white powder; Mp >300 °C; (KBr, cm^{-1}): 3408, 3155 (N-H), 3060, 2897, 1632 (CONH), 1550, 1226 (C-N), 1029 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6): δ= 12.07 (brs, 2H, NH), 11.85 (brs, 2H, NH), 6.81 (d, 1H, J = 8.4 Hz, H_{Ar}), 6.78 (brs, 1H, H_{Ar}), 6.64 (brs, 1H, NH), 6.59 (d, 1H, J = 8.4 Hz, H_{Ar}), 5.31 (brs, 1H, CH), 3.71 (s, 3H, MeO), 3.66 (s, 3H, MeO). ^{13}C NMR (100 MHz, DMSO-d_6): δ= 173.2, 172.6 (C=S), 163.5, 162.3 (C=O), 154.9, 153.9, 148.8, 147.3, 130.7, 118.9, 111.8, 111.6, 91.0, 78.7, 56.0 (OMe), 55.9 (OMe), 32.5. Anal. Calculated for $C_{17}H_{15}N_5O_4S_2$ (417.46), Found: C, 48.84; H, 3.53; N, 16.71 requires C, 48.91; H, 3.62; N, 16.78%);

4.2.10 2,8-Dithioxopyrido-5-(4-methylphenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3j)

Yield 75%: White powder; Mp >300 °C; (KBr, cm^{-1}): 3333, 3173 (N-H), 2898, 1605 (CONH), 1544, 1228 (C-N), 1167 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.08 (brs, 2H, NH), 11.85 (brs, 2H, NH), 7.03 (d, 2H, J = 8.2 Hz, H_{Ar}), 6.96 (d, 2H, J = 8.2 Hz, H_{Ar}), 6.79 (brs, 1H, NH), 5.31 (s, 1H, CH), 2.25 (s, 3H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.2, 172.6 (C=S), 163.5, 161.5 (C=O), 153.8, 151.3, 149.5, 135.1, 134.6, 129.0, 126.9, 124.0, 90.8, 89.8, 32.5, 21.5 (Me). Anal. Calculated for $C_{16}H_{13}N_5O_2S_2$ (371.44), Found: C, 51.66; H, 3.43; N, 18.75 requires C, 51.74; H, 3.53; N, 18.85%.

4.2.11 2,8-Dithioxopyrido-5-(3-methoxylphenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3k)

Yield 72%: White powder; Mp >300 °C; (KBr, cm^{-1}): 3402, 3155 (N-H), 3035 2956, 1694 (CONH), 1549, 1453, 1215 (C-N), 1173 (C=S), 1043 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6): δ= 12.05 (s, br., 2H),

11.83 (s, br., 2H), 7.13 (t, J = 7.9 Hz, 1H, H_{Ar}), 6.76 (s, br., 1H, H_{Ar}), 6.71-6.64 (m, 2H, H_{Ar}), 6.58 (s, 1H, NH), 5.30 (s, 1H, CH), 3.66 (s, 3H, OMe). ^{13}C NMR (100 MHz, DMSO-d_6): δ= 172.8, 172.0 (C=S), 163.0, 159.2 (C=O), 153.4, 139.8, 128.9, 118.9, 112.9, 110.9, 108.0, 90.3, 54.9, 32.4. Anal. Calculated for $C_{16}H_{13}N_5O_3S_2$ (387.44), Found: C, 49.53; H, 3.25; N, 18.19 requires C, 49.60; H, 3.38; N, 18.08%.;

4.2.12 2,8-Dithioxopyrido-5-(phenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3l)

Yield 70%; white powder; Mp >300 °C; (KBr, cm^{-1}): 3404, 3323, 3155 (N-H), 2962, 2896, 613 (CONH), 1550, 1444, 1287 (C-N), 1183 (C=S); ^{1}H NMR (400 MHz, DMSO-d6): δ(ppm) = 11.88 (brs, 2H, NH), 11.67 (brs, 2H, NH), 7.24 (t, 1H, J = 7.4 Hz, H_{Ar}), 7.15-7.08 (m, 2H, H_{Ar}), 6.80 (brs, 1H, NH), 5.35 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.2, 172.6 (C=S), 163.5, 162.3 (C=O), 154.9, 153.9, 138.3, 129.7, 128.8, 121.9, 90.7, 78.6, 32.9. Anal. Calculated for $C_{15}H_{11}N_5O_2S_2$ (357.41), Found: C, 50.33; H, 3.02; N, 19.45 requires C, 50.41; H, 3.10; N, 19.59%.

4.2.13 2,8-Dithioxopyrido-5-(1-naphtyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3m)

Yield 73%: white powder; Mp >300 °C; (KBr, cm^{-1}): 3425, 3323 (N-H), 3082, 2969, 1634 (CONH), 1551, 1438, 1294 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.01 (m, 4H, NH), 7.91 (d, 1H, J = 7.2, 1.8 Hz, H_{Ar}), 7.78-7.74 (m, 1H, H_{Ar}), 7.67 (d, 1H, J = 6.8, 1.2 Hz, H_{Ar}), 7.50-7.48 (m, 2H, H_{Ar}), 7.47 (t, J = 8.0 Hz, 1H, H_{Ar}), 7.33 (d, 1H, J = 7.6 Hz, H_{Ar}), 6.64 (brs, 1H, NH), 5.80 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.1, 173.0 (C=S), 163.5, 163.1 (C=O), 154.0, 153.4, 131.7, 131.3, 130.2, 129.6, 129.2, 129.2, 127.4, 127.2, 126.2, 125.9, 90.2, 89.8, 31.7. Anal. Calculated for $C_{19}H_{13}N_5O_2S_2$ (407.47), Found: C, 55.93; H, 3.12; N, 17.05 requires C, 56.01; H, 3.22; N, 17.19%.

4.2.14 2,8-Dithioxopyrido-5-(2-chlorophenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3n)

Yield 75%: White powder; Mp >300 °C; (KBr, cm^{-1}): 3394, 3340, 3128 (N-H), 3041, 2954, 1646 (CONH), 1549, 1279 (C-N), 1169 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.07 (brs, 2H, NH), 11.93 (brs, 2H, NH), 7.34-7.18 (m, 4H, H_{Ar}), 6.60 (brs, 1H, NH), 5.31 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.2, 173.1 (C=S), 163.5, 162.3 (C=O), 153.5, 153.5, 137.4, 132.8, 130.0, 129.4, 128.0, 127.1, 90.2, 78.6, 32.4. Anal. Calculated for $C_{15}H_{10}ClN_5O_2S_2$ (391.86), Found: C, 45.81; H, 2.35; N, 17.61 requires C, 45.98; H, 2.57; N, 17.87%.

4.2.15 2,8-Dithioxopyrido-5-(2-hydroxyphenyl)-5,10-dihydropyrido[2,3-d:5,6-d']dipyrimidine-4,6(3H,7H)-dione (3o)

Yield 70%: White powder; Mp >300 °C; (KBr, cm^{-1}): 3434 (O-H), 3308 (N-H), 3055 2963, 1648 (CONH), 1459, 1222 (C-N and C-O); ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) = 12.32 (brs, 2H, NH), 11.59, 11.51 (brs, 2H, NH), 7.24-7.20 (m, 1H, H_{Ar}), 7.13-7.09 (m, 2H, H_{Ar}), 6.99 (d, J = 8.4 Hz, 1H, H_{Ar}), 6.77 (brs, 1H, NH), 4.91 (s, 1H, CH), 4.71 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ(ppm) = 173.6, 173.6 (C=S), 161.5, 160.6 (C=O), 154.6, 151.3, 149.5, 129.9, 129.1, 128.3, 125.5, 124.0, 93.9, 91.6, 27.1. Anal. Calculated for $C_{15}H_{11}N_5O_3S_2$ (373.41), Found: C, 48.13; H, 3.08; N, 18.87 requires C, 48.25; H, 2.97; N, 18.76%.

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References

1. B. Karami, S. J. Hoseini, Kh. Eskandari, A. Ghasemi and H. Nasrabadi, "Synthesis of xanthene derivatives by employing Fe_3O_4 nanoparticles as an effective and magnetically recoverable catalyst in water", *Catalysis Science & Technology*, vol. 2, pp. 331-338, 2012.

2. H. Ebrahimzadeh, E. Moazzen, M. M. Amini and O. Sadeghi, "Novel magnetic ion imprinted polymer as a highly selective sorbent for extraction of gold ions in aqueous samples", *Analytical Methods*, vol. 4, pp. 3232-3237, 2012.
3. M. Esmaeilpour, A. R. Sardarian and J. Javidi, "Schiff base complex of metal ions supported on superparamagnetic Fe_3O_4@SiO_2 nanoparticles: An efficient, selective and recyclable catalyst for synthesis of 1,1-diacetates from aldehydes under solvent-free conditions", *Applied Catalysis*, A, vol. 445-446, pp. 359-367, 2012.
4. K. K. Senapati, C. Borgohain and P. Phukan, "Synthesis of highly stable $CoFe_2O_4$ nanoparticles and their use as magnetically separable catalyst for Knoevenagel reaction in aqueous medium", *Journal of Molecular Catalysis A Chemical*, vol. 339, no. 1, 24-31, 2011.
5. D. Habibi, S. Kaamyabi and H. Hazarkhani, "Fe_3O_4 nanoparticles as an efficient and reusable catalyst for the solvent-free synthesis of 9,9-dimethyl-9,10-dihydro-8H-benzo-[a]xanthen-11(12H)-ones", *Chinese Journal of Catalysis*, vol. 36, no. 3, pp. 362-366, 2015.
6. A. Hu, G. T. Yee and W. Lin, "Magnetically recoverable chiral catalysts Immobilized on magnetite nanoparticles for asymmetric hydrogenation of aromatic ketones", *Journal of the American Chemical Society*, vol. 127, no. 36, pp. 12486–12487, 2005.
7. C. W. Lim and I. S. Lee, "Magnetically recyclable nanocatalyst systems for the organic reactions",*Nano Today*, vol. **5**, pp. 412-434, 2010.
8. S. Rostamnia, K. Lamei, M. Mohammadquli, M. Sheykhan and A. Heydari, "Nanomagnetically modified sulfuric acid (γ-Fe_2O_3@SiO_2-OSO_3H): An efficient, fast, and reusable green catalyst for the Ugi-like Groebke-Blackburn-Bienaymé three-component reaction under solvent-free conditions", *Tetrahedron Letters*, vol. 53, no. 39, pp. 5257-5260, 2012.
9. Y. Zhang, Y. Zhao and C. Xia, "Basic ionic liquids supported on hydroxyapatite-encapsulated γ-Fe_2O_3 nanocrystallites: An efficient magnetic and recyclable heterogeneous catalyst for aqueous Knoevenagel condensation", *Journal of Molecular Catalysis A: Chemical*, vol. 306, no.1–2, pp. 1-148, 2009.
10. L. Ma'mani, M. Sheykhan and A. Heydari, "Nanosilver embedded on hydroxyapatite-encapsulated γ-Fe_2O_3: Superparamagnetic catalyst for chemoselective oxidation of primary amines to N-monoalkylated hydroxylamines", *Applied Catalysis A: General*, vol. 395, no. 1–2, pp. 34-38, 2011.
11. L. Ma'mani, M. Sheykhan, A. Heydari, M. Faraji and Y. Yamini, "Sulfonic acid supported on hydroxyapatite-encapsulated-γ-Fe_2O_3 nanocrystallites as a magnetically Brønsted acid for N-formylation of amines", *Applied Catalysis A: General*, vol. 377, no.1–2, pp. 64–69, 2010.
12. M. Khoobi, L. Ma'mani, F. Rezazadeh, Z. Zareie and A. Foroumadi, "One-pot synthesis of 4H-benzo[b]pyrans and dihydropyrano[c]chromenes using inorganic–organic hybrid magnetic nanocatalyst in water", *Journal of Molecular Catalysis A: Chemical*, vol. 359, pp. 74-80, 2012.
13. A. Rahmati, "Synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7-tetrahydro-2H-pyrazolo [3,4-b] pyridine-5-carbonitrile via a one-pot, three-component reaction", *Tetrahedron Letters*, vol.51, no. 22, pp. 2967-2970, 2010.
14. D. Q. Shi, S. H. Shi, Z. B. Kim and S. J. Huang, "A novel and efficient one-pot synthesis of furo[3′ ,4′ :5,6]pyrido[2,3-c]pyrazole derivatives using organocatalysts", *Tetrahedron*, vol. 64, no. 10, pp. 2425–2432, 2008.
15. A. D. Broom, J. L. Shim and G. L. Anderson, "Pyrido[2,3-d]pyrimidines. IV. Synthetic studies leading to various oxopyrido[2,3-d]pyrimidines" *The Journal of Organic Chemistry*, Vol. 41, no. 7, pp. 1095-1099, 1976.
16. E. M. Grivsky, S. Lee, C. W. Sige, D. S. Duch and C. A. Nichol, "Synthesis and antitumor activity of 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-d] pyrimidine ", *Journal of Medicinal Chemistry*, vol. 23, no. 3, pp. 327–329, 1980.
17. J. Matsumoto and S. Minami, "Pyrido[2,3-d]pyrimidine antibacterial agents. 3. 8-Alkyl- and 8-vinyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]pyrimidine-6-carboxylic acids and their derivatives", *Journal of Medicinal Chemistry*, vol. 18, no. 1, pp. 74–79, 1975.
18. A. M. Thompson, G. W. Rewcastl, A. J. Bridge, D. W. Fry, A. J. Kraker, W. A. Denny and A. McMichael, "Tyrosine kinase inhibitors. 7. 7-amino-4-(phenylamino)- and 7-amino-4-[(phenylmethyl)amino]pyrido[4,3-d]pyrimidines: a new class of inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor", *Journal of Medicinal Chemistry*, Vol. 38, no. 19, pp 3780–3788, 1995.
19. N. R. Mohamed, M. M. T. El-Saidi, Y. M. Ali and M. H. Elnagdi, "Utility of 6-amino-2-thiouracil as a precursor for the synthesis of bioactive pyrimidine derivatives", *Bioorganic & Medicinal Chemistry*, vol. 15, no. 18, pp. 6227–6235, 2007.

20. A. Pastor, R. Alajarin, J. J. Vaquero, J. Alvarez-Builla, M. Fau de Casa-Juana, C. Sunkel, J. G. Priego, I. Fonseca and J. Sanz-Aparicio, "Synthesis and structure of new pyrido [2, 3-d] pyrimidine derivatives with calcium channel antagonist activity", *Tetrahedron*, vol. 50, no. 27, pp. 8085–8098, 1994.
21. A. B. A. Elgazzar, A. E. M. Gafaar, H. N. Hafez and A. S. Aly, "Novel syntheses and reactions of polynuclear heterocyclic derivatives derived from thioxopyridopyrimidine, with a new ring system", *Phosphorus, Sulfur, and Silicon and the Related Elements*, vol.181, no. 8, pp. 1859-1883, 2006.
22. M. S. Youssouf, P. Kaiser, G. D. Singh, S. Singh, S. Bani, V. K. Gupt, N. K. Satti, K. A. Suri and R. K. Johri, "Anti-histaminic, anti-inflammatory and bronchorelaxant activities of 2, 7-dimethyl-3-nitro-4H pyrido [1,2-a] pyrimidine-4-one", *International Immunopharmacology*, vol. 8, no. 7, pp. 1049-1055, 2008.
23. A. B. A. El-Gazzar, M. M. Youssef, A. A. Abu-Hashem and F. A. Badria, "Synthesis and anti-oxidant activity of novel pyrimido [4, 5-b] quinolin-4-one derivatives with a new ring system", *Phosphorus, Sulfur, and Silicon and the Related Elements*, vol. 182, no. 9, pp. 2009-2037, 2007.
24. M. R. Mahmoud, E. A. A. El-Bordany, N. F. Hassan and F. S. M. Abu El-Azm, "Utility of nitriles in synthesis of pyrido[2,3-d]pyrimidines, thiazolo[3,2-a]pyridines, Pyrano[2,3-b]benzopyrrole, and Pyrido[2,3-d]benzopyrroles", *Phosphorus, Sulfur, and Silicon and the Related Elements*, vol. 182, no. 11, pp. 2507-2521, 2007.
25. J. Bulicz, C. G. Daniela, D. C. G. Bertarelli, D. Baumert, F. Fülle, C. E. Müller and D. Heber, "Synthesis and pharmacology of pyrido[2,3-d]pyrimidinediones bearing polar substituents as adenosine receptor antagonists", *Bioorganic & Medicinal Chemistry*, vol. 14, no. 8, pp. 2837-2849, 2006.
26. J. I. Degraw, P. H. Christie, W. T. Colwell and F. M. Sirotnak, "Synthesis and antifolate properties of 5,10-ethano-5,10-dideazaaminopterin", *Journal of Medicinal Chemistry*, vol. 35, no. 2, pp 320–324, 1992.
27. A. D. Broom, J. L. Shim and G. J. Anderson, "Pyrido[2,3-d]pyrimidines. IV. Synthetic studies leading to various oxopyrido[2,3-d]pyrimidines", *The Journal of Organic Chemistry*, vol. 41, no. 7, pp. 1095-1099, 1976.
28. I. Devi, J. L. Borah and P. L. Bhuyan, "A novel three-component one-pot synthesis of pyrano[2,3-d]pyrimidines and pyrido[2,3-d]pyrimidines using microwave heating in the solid state", *Tetrahedron Letters*, vol. 44, no. 45, pp. 8307-8310, 2003.
29. Y. Gao, S. J. Tu, T. J. Li, X. J. Zhang, S. L. Zhu, F. Fang, D. Q. Shi, "Effective synthesis of 7-amino-6-cyano-5-aryl-5H-pyrano[2,3-d] pyrimidine-2,4(1H,3H)- diones Under Microwave Irradiation", *Synthetic Communications*, Vo. 34, no. 7, pp. 1295-1299, 2004.
30. J. Quiroga, M. Alvarado, B. Insuasty, M. Nogueras, A. Sanchez and J. Cobo, "Synthesis of 6-cyanopyrido[2,3-d]pyrimidinones in the reaction of 6-amino-4-pyrimidinones with arylidene derivatives of malonodinitrile", *Journal of Heterocyclic Chemistry*, vol. 35, no. 6, pp. 1309–1311, 1998.
31. S. Abdolmohammadi and S. Balalaie, "An Efficient Synthesis of Pyrido[2,3-d]pyrimidine Derivatives via One-Pot Three-Component Reaction in Aqueous Media", *International Journal of Organic Chemistry*, vol. 2 no. 1, 1-8, 2012.
32. X.-S. Wang, Z.-S. Zeng, D.-Q. Shi, X.-Y. Wei and Z.-M. Zong, "KF-Alumina catalyzed one-pot Synthesis of pyrido[2,3-d]pyrimidine derivatives", *Synthetic Communications*, Vol. 34, no.23, pp. 4331-4338, 2004.
33. X.-S. Wang, Z.-S. Zeng, D.-Q. Shi, S. Tu, S.-J.; X. –Y. Wei and Z.-M. Zong, "Three-Component, one-pot Synthesis of pyrido[2,3-d]pyrimidine derivatives catalyzed by KF-alumina", *Synthetic Communications*, vol. 36, no. 14, pp.1921-1927, 2005.
34. M. Syamala, "Recent Progress in Three-Component Reactions. An Update", *Organic Preparations and Procedures International*, vol. 41, no. 1, pp. 1-68, 2009.
35. D. Shi, S. Ji, L. Niu, J. Shi and X. Wang, "One-pot synthesis of pyrido[2,3-d]pyrimidines via efficient three-component reaction in aqueous media", *Journal of Heterocyclic Chemistry*, vol. 44, no.5, pp. 1083–1090, 2007.
36. D-Q. Shi, Y. Zhou and H. Liua, "An efficient synthesis of pyrido[2,3-d]pyrimidine derivatives in ionic liquid", *Journal of Heterocyclic Chemistry*, vol. 47, no. 1, pp. 131–135, 2010.
37. M. Mamaghani, F. Shirini, M. Sheykhan and M. Mohsenimehr, "Synthesis of a copper(II) complex covalently anchoring a (2-iminomethyl)phenol moiety supported on HAp-encapsulated-a-Fe_2O_3 as an inorganic–organic hybrid magnetic nanocatalyst for the synthesis of primary and secondary amides" *Royal Society of Chemistry Advances*, vol. 5, pp. 44524–44529, 2015.

38. M. Mamaghani, F. Shirini, N. O. Mahmoodi, A. Azimi-Roshan and H. Hashemlou, “A green, efficient and recyclable Fe^{+3}@K10 catalyst for the synthesis of bioactive pyrazolo[3,4-b]pyridin-6(7H)-ones under "on water", conditions”, *Journal of Molecular Structure*, vol. 1051, pp. 169–176, 2013.
39. M. Mamaghani, Z. Taati, M. Rasoulian, J. Yousefizad, N. Toraji, M. Mohsenimehr and R. Hossein Nia, “[Fe_2O_3@HAp-SO_3H] an efficient nanocatalyst for the synthesis of highly functionalised 2-thioxopyrido[2,3-d]pyrimidines”, *Journal of Chemical Research*, vol. 40, pp. 29–34, 2016.
40. R. Hossein Nia, M. Mamaghani, K. Tabatabaeian, F. Shirini and M. Rassa, “An expeditious regioselective synthesis of novel bioactive indole-substituted chromene derivatives via one-pot three-component reaction”, *Bioorganic and Medicinal Chemistry Letters*, vol. 22, pp. 5956–5960, 2012.
41. P. Crepaldi, B. Cacciari, M. C. Bonache, K. Varani, P. A. Borea, Iv. Kügelgen, K. Hoffmann, M. Pugliano, C. Razzari and M. Cattaneo, “6-Amino-2-mercapto-3H-pyrimidin-4-one derivatives as new candidates for the antagonism at the $P2Y_{12}$ receptors”, *Bioorganic and Medicinal Chemistry*, vol. 17, no. 13, pp. 4612-4621, 2009.

