J. Chem. Sci. Vol. 127, No. 11, November 2015, pp. 1895–1904.
DOI 10.1007/s12039-015-0964-1

One-pot synthesis of novel pyrimido[4,5-*b*]quinolines and pyrido[2,3-*d*:6,5*d*′]dipyrimidines using encapsulated-γ-Fe_2O_3 nanoparticles

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MS received 24 December 2014; revised 26 July 2015; accepted 30 July 2015

Abstract. Novel pyrimido[4,5-*b*]quinolines and pyrido[2,3-*d*:6,5-*d*′]dipyrimidine derivatives were synthesized in one-pot, three-component approach using sulfonic acid supported on hydroxyapatite-encapsulated-γ-Fe_2O_3 [γ-Fe_2O_3@HAp-SO_3H] as magnetically recoverable nanocatalyst. The protocol provided a rapid, useful and green method for the preparation of the products in short reaction times and high yields.

Keywords. Pyrimido[4,5-*b*]quinoline; pyrido[2,3-*d*:6,5-*d*′]dipyrimidine; three-component reaction; one-pot; [γ-Fe_2O_3@HAp-SO_3H]; nanocatalyst.

1. Introduction

Recently, the development of new strategies for non-toxic, sustainable, low cost, eco-friendly, recyclable catalytic systems with high efficiency has received growing interest in organic synthesis for reasons of economy and environmental impact. In this respect, nanoparticles (NPs) have appeared as a bridge between homogeneous and heterogeneous catalysts.[1] To further address the issues of recyclability and reusability, magnetic nanoparticles (MNPs) as heterogeneous catalyst have gained effective role in organic synthesis.[2] Due to their magnetic properties they are easily separated from the reaction mixture by an external magnet. MNPs as solid acid catalyst have served as important functional materials in industrial processes. A few examples can be cited as, designing different Brønsted acids ($ClSO_3H$, $HClO_4$, HBF_4) on γ-Fe_2O_3@SiO_2[3–6] and functionalized hydroxyapatite-encapsulated-γ-Fe_2O_3 magnetic nanoparticles.[7–11] Furthermore, the catalytic properties of Fe_2O_3 NPs have been nicely exploited in various reactions,[12] such as oxidation of olefins and alcohols using O_2 or hydrogen peroxide,[13] direct borylation of arenes,[14] formation of 2-phenylquinazoline derivatives *via* condensation of benzylamine with 2-aminoaryl ketones[15] and C-H activation. SiO_2 supported γ-Fe_2O_3 NPs has also been introduced for drug delivery and magnetic targeting systems.[16]

On the other hand, heterocyclic molecules are an important class of compounds, making up more than half of all known organic compounds, especially nitrogen heterocycles which are present in a wide variety of natural products and medicinal chemistry.[17] Fused heterocyclic systems, incorporating a pyrimidine ring in their structures, play important roles in various biological and pharmaceutical activities,[18–22] such as antifungal, antibacterial, anti-inflammatory, anticancer, and cardio protective effects. In particular, pyrimidoquinoline derivatives have been used in a number of biologically active compounds with anticancer,[23] antimicrobial,[24] antimalarial,[25] and anti inflammatory activities.[26] These observations led us to attempt the synthesis of some new pyrimidine derivatives using 6-amino-2-(ethylthio or butylthio)pyrimidin-4(3*H*)-one (**1, 5**) as starting material and [γ-Fe_2O_3@HAp-SO_3H] as recyclable nanocatalyst.

2. Experimental

2.1 *General information*

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker

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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. Elemental analyses were performed on a Carlo-Erba EA1110CNNO-S analyzer and agreed (within 0.3%) with the calculated values. XRD was carried out on a Philips X-PertMPD diffractometer using Cotube. Scanning electron microphotographs (SEM) which 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.

2.2 *General procedure for the synthesis of pyrimido [4,5-b]quinolines derivatives (**4a-j**)*

[γ-Fe_2O_3@HAp-SO_3H] was synthesized according to the reference.[7] Then, to a mixture of 6-amino-2-ethylthio pyrimidin-4(3*H*)-one **1** (1 mmol), dimedone **2** (1 mmol) and arylaldehydes **3** (1 mmol) in EtOH (1 mL) [γ-Fe_2O_3@HAp-SO_3H] (10 mg, 0.9 mol%) were added and the reaction mixture was stirred at 60°C. After completion of the reaction, which was monitored by TLC, 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 washed with ethanol and recrystallized from appropriate solvent to furnish the desired pure product (**4a-j**).

2.3 *General procedure for the synthesis of pyrido [2,3-d:6,5-d′]dipyrimidines derivatives (**7a-n**)*

A mixture of butylthiopyrimidin-4(3*H*)-one (**1**) (2 mmol), arylaldehyde (1 mmol) and [γ-Fe_2O_3@HAp-SO_3H] (0.02 g) in DMF (1 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with H_2O and the catalyst was easily separated by an external magnet. The crude solid product was washed with THF to produce pure pyridodipyrimidines **7a-n**.

2.4 *6-Amino-2-(ethylthio)pyrimidine-4(3H)-one (**1**)*

Yield 98%; White powder, M.p. >300°C; IR (KBr): 3462, 3275, 3195 (N-H),1658 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 11.45 (s, br., 1H, NH), 6.44 (s, br., 2H, NH_2), 4.90 (s, 1H), 3.05 (q, J = 7.2 Hz, 2H, CH_2), 1.28 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 164.6 (C=O, amide), 164.0, 162.6, 81.7, 24.2 (CH_2), 15.2 (CH_3).

2.4a *5-(2,4-Dichlorophenyl)2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (**4a**)*: Yield 94%; White powder, M.p. 310-313°C; IR (KBr): 3255, 3184 (N-H),1651(CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.25 (s, br., 1H, NH), 9.84 (s, 1H, NH), 7.35 (s, 1H, Ar-H), 7.32-7.25 (m, 2H, Ar-H), 5.17 (s, 1H, H_b), 3.14 (q, J = 7.2 Hz, 2H, CH_2), 2.49-2.38 (diasteretopic protons, AB q., J = 17.2 Hz, 2H, H_c), 2.17, 1.95 (diasteretopic protons, AB q., J = 16.2 Hz, 2H, H_d), 1.31 (t, J = 7.2, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.3, 161.0 (C=O), 152.0, 151.9, 143.2, 133.8, 133.7, 131.2, 128.7, 127.1, 126.0 109.0, 97.5, 50.6, 34.1, 32.4, 29.5, 27.0, 24.6, 15.1; Anal. Calc. (%) for $C_{21}H_{21}Cl_2N_3O_2S$ (450.4): C, 56.00; H, 4.70; N, 9.33; Found: C, 56.18 ; H, 4.81 ; N, 9.12%.

2.4b *5-(2-Chlorophenyl)-2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (**4b**)*: Yield 95%; White powder, M.p. 296-298°C; IR (KBr): 3250, 3180 (N-H), 1643 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.19 (s, br., 1H, NH), 9.80 (s, 1H, NH), 7.31 (d, J = 6.4 Hz, 1H, Ar-H), 7.23 (d, J = 8.0 Hz, 1H, Ar-H), 7.18 (t, J = 7.4 Hz, 1H, Ar-H), 7.09 (dt, J = 7.6, 1.2 Hz, 1H, Ar-H), 5.20 (s, 1H, H_b), 3.13 (q, J = 7.2 Hz, 2H, CH_2), 2.49, 2.38 (diasteretopic protons, AB q., J = 16.8 Hz, 2H, H_c), 2.16, 1.94 (diasteretopic protons, AB q., J = 15.8 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.2 , 161.1(C=O), 151.8, 151.6, 144.2, 132.9, 132.5, 129.5, 127.8, 127.7, 126.9, 109.4 , 97.8, 50.6, 34.2, 32.4, 29.6, 27.0, 24.5, 15.1; Anal. Calc. (%) for $C_{21}H_{22}ClN_3O_2S$ (415.9): C, 60.64; H, 5.33; N, 10.10; Found: C, 60.48; H, 5.17; N, 10.18%.

2.4c *5-(4-Chlorophenyl)2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinolone-4,6(3H,5H,7H,10H)-dione (**4c**)*: Yield 95%; White powder, M.p. 318-320°C; IR (KBr): 3248, 3175 (N-H),1645 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.34 (s, br., 1H, NH), 9.82 (s, 1H, NH), 7.26 (d, J = 8.2 Hz, 2H, Ar-H), 7.20 (t, J = 8.2 Hz, 2H, Ar-H), 4.88 (s, 1H, H_b), 3.13 (q, J = 7.2 Hz, 2H, CH_2), 2.50, 2.44 (diasteretopic protons, AB q., J = 17.2 Hz, 2H, H_c), 2.16, 1.94 (diasteretopic protons, AB q., J = 16.0 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.90 (s, 3H,CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C:194.5, 161.2 (C=O), 152.1, 151.6, 146.0, 130.8, 129.9, 128.2, 109.7, 98.1, 50.6, 33.9, 32.6, 29.4, 27.2, 24.5, 15.1; Anal. Calc. (%) for $C_{21}H_{22}ClN_3O_2S$ (415.9):

C, 60.64; H, 5.33; N, 10.10; Found: C, 60.52; H, 5.15; N, 10.02%.

2.4d *5-(3-Chlorophenyl)2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (**4d**)*: Yield 91%; White powder, M.p. 347-349°C; IR (KBr): 3225, 3165 (N-H),1653 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.37 (s, br., 1H, NH), 9.84 (s, 1H, NH), 7.25 (d, J = 7.8 Hz,1H, Ar-H), 7.21 (s, 1H, Ar-H), 7.17-7.13 (m, 2H,Ar-H), 4.89 (s, 1H, H_b), 3.14 (q, J = 7.2 Hz, 2H, CH_2), 2.51, 2.46 (diasteretopic protons, AB q., J = 17.2 Hz, $2H_c$, H_c), 2.16, 1.94 (diasteretopic protons, AB q., J = 16.2 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.4, 162.0 (C=O), 152.5, 151.9, 151.8, 149.3, 132.8, 130.3, 127.9, 126.6, 126.3, 109.4, 97.9, 50.5, 34.3, 32.6, 29.4, 27.1, 24.6, 15.1; Anal. Calc. (%) for $C_{21}H_{22}ClN_3O_2S$ (415.9): C, 60.64; H, 5.33; N, 10.10; Found: C, 60.52; H, 5.20; N, 10.16%.

2.4e *5-(4-Nitrophenyl)-2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinolone-4,6(3H,5H,7H,10H)-dione (**4e**)*: Yield 85%; White powder, M.p. 336-338°C; IR (KBr): 3265, 3182 (N-H),1645 (CONH) cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.39 (s, br., 1H, NH), 9.92 (s, 1H, NH), 8.10 (d, J = 8.6 Hz, 2H, Ar-H), 7.47 (t, J = 8.6 Hz, 2H, Ar-H), 5.00 (s, 1H, H_b), 3.14 (q, J = 7.2 Hz, 2H, CH_2), 2.53, 2.46 (diasteretopic protons, AB q., J = 17.2 Hz, $2H_c$, H_c), 2.21, 2.02 (diasteretopic protons, AB q., J = 16.0 Hz, 2H, H_d), 1.31 (t, J = 7.2, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.4, 161.2 (C=O), 154.4, 152.2, 152.1, 146.2, 129.4, 123.6, 109.0, 97.5, 50.5, 35.0, 32.6, 29.4, 27.2, 24.6, 15.1; Anal. Calc. (%) for $C_{21}H_{22}N_4O_4S$ (426.50): C, 59.14; H, 5.20; N, 13.14; Found: C, 59.03; H, 5.08; N, 13.20%.

2.4f *5-(2-Boromophenyl)2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (**4f**)*: Yield 84%; White powder, M.p. 339-341°C; IR (KBr): 3254, 3182 (N-H), 1643(CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.17 (s, br., 1H, NH), 9.80 (s, 1H, NH), 7.40 (d, J = 8.0 Hz, 1H, Ar-H), 7.28 (d, J = 6.4 Hz, 1H, Ar-H), 7.22 (t, J = 7.4 Hz, 1H, Ar-H),7.00 (dt, J = 7.6, 1.2 Hz,1H, Ar-H), 5.19 (s, 1H, H_b), 3.14 (q, J = 7.2 Hz, 2H, CH_2), 2.49, 2.39 (diasteretopic protons, AB q., J = 17.2 Hz, 2H, H_c), 2.16, 1.94 (diasteretopic protons, AB q., J = 16.0 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.2, 162.0 (C=O), 152.9, 151.6, 151.5, 146.1, 132.**8**, 132.3, 127.9, 127.6, 123.4, 109.9, 98.3, 50.7, 36.2, 32.4, 29.5, 27.1, 24.5, 15.1; Anal. Calc. (%) for $C_{21}H_{22}BrN_3O_2S$ (460.4): C, 54.79; H, 4.82; N, 9.13; Found: C, 54.60; H, 4.71; N, 9.01%.

2.4g *5-(2-Fluorophenyl)2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (**4g**)*: Yield 92%; White powder, M.p. 298-300°C; IR (KBr): 3437, 3248, 3180 (N-H),1650 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.24 (s, br., 1H, NH), 9.80 (s, 1H, NH), 7.24 (t,J = 7.4 Hz,1H, Ar-H), 7.12 (dd, J = 6.8, 5.6 Hz, 1H, Ar-H), 7.04-6.94 (m, 2H, Ar-H), 5.06 (s, 1H, H_b), 3.13 (q, J = 7.2 Hz, 2H, CH_2), 2.49, 2.39 (diasteretopic protons, AB q., J = 17.2 Hz, 2H, H_c), 2.18, 1.96 (diasteretopic protons, AB q., J = 16.2 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.2, 162.0, 160.3 (d, $^1J_{CF}$ = 245.0 Hz), 152.2, 151.6, 133.8, 133.6, 131.5 (d, $^4J_{CF}$ = 4.0 Hz), 128.1 (d, $^3J_{CF}$ = 8.0 Hz), 124.1, 115.4 (d, $^2J_{CF}$ = 22.0 Hz), 109.0, 98.0, 50.6, 32.5, 30.0, 29.6, 26.8, 24.5, 15.1; Anal. Calc. (%) for $C_{21}H_{22}FN_3O_2S$ (399.5): C, 63.14; H, 5.55; N, 10.52; Found: C, 63.20; H, 5.45; N, 10.39%.

2.4h *5-(4-Fluorophenyl)2-(ethylthio)-8,9-dihydro-8,8-dimethylpyrimido[4,5-b]quinolone-4,6(3H,5H,7H,10H)-dione (**4h**)*: Yield 92%; White powder, M.p. 314-31°C; IR (KBr): 3250, 3176 (N-H), 1645(CONH) cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.33 (s, br., 1H, NH), 9.80 (s, 1H, NH), 7.21 (m, 2H, Ar-H), 7.02 (t, J = 8.6 Hz, 2H, Ar-H), 4.90 (s, 1H, H_b), 3.31 (q, J = 7.2 Hz, 2H, CH_2), 2.50, 2.44 (diasteretopic protons, AB q., J = 17.2 Hz, 2H, H_c), 2.20, 2.02 (diasteretopic protons, AB q., J = 16.2 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.5, 162.1 (C=O), 161.0 (d, $^1J_{CF}$ = 240.0 Hz), 151.6, 151.4, 143.2, 134.1, 129.7 (d, $^3J_{CF}$ = 8.0 Hz), 114.9 (d, $^2J_{CF}$ = 21.0 Hz), 109.9, 97.5, 50.6, 33.5, 32.6, 29.4, 27.2, 24.5, 15.1; Anal. Calc. (%) for $C_{21}H_{22}FN_3O_2S$ (399.5): C, 63.14; H, 5.55; N, 10.52; Found: C, 63.01; H, 5.43; N, 10.41%.

2.4i *2-(Ethylthio)-8,9-dihydro-8,8-dimethyl-5-phenylpyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (**4i**)*: Yield 89%; White powder, M.p. 317-320°C; IR (KBr): 3220, 3155 (N-H), 1653 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.30 (s, br., 1H, NH), 9.77 (s,

1H, NH), 7.20-7.17 (m, 4H, Ar-H), 7.07-7.10 (m, 1H, Ar-H), 4. 90 (s, 1H, H_b), 3.13 (q, J = 7.2 Hz, 2H, CH_2), 2.50, 2.45 (diasteretopic protons, AB q., J = 17.2 Hz, 2H_c, H_c), 2.20, 2.03 (diasteretopic protons, AB q., J = 16.2 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.4, 162.0 (C=O, amide), 152.8, 151.5, 151.2, 147.0, 128.2 128.0, 126.3, 110.0, 50.7, 34.0, 32.6, 29.5, 27.2, 24.5, 15.1; Anal. Calc. (%) for $C_{21}H_{23}N_3O_2S$ (381.5): C, 66.12; H, 6.08; N, 11.01; Found: C, 66.03; H, 6.17; N, 10.88%.

2.4j *2-(Ethylthio)-8,9-dihydro-8,8-dimethyl-5-(thiophen-2-yl)pyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (**4j**)*: Yield 95%; White powder, M.p. 298-301°C; IR (KBr): 3207, 3163 (N-H),1639 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.43 (s, br., 1H, NH), 9.90 (s, 1H, NH), 7.18 (d, J = 5.2 Hz,1H, Ar-H), 6.83 (dd, J = 4.8, 3.6 Hz,1H, Ar-H), 6.74 (d, J = 2.8 Hz,1H, Ar-H) 5.23 (s, 1H, H_b), 3.14 (q, J = 7.2 Hz,2H, CH_2), 2.50, 2.43 (diasteretopic protons, AB q., J = 17.6 Hz, 2H, H_c), 2.24, 2.10 (diasteretopic protons, AB q., J = 16.2 Hz, 2H, H_d),1.31 (t, J = 7.2, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.4, 161.9 (C=O), 152.2, 152.5, 151.7, 151.6, 150.9, 126.9, 123.8, 123.5, 109.6, 97.9, 50.6, 32.6, 29.6, 28.7, 27.2, 24.6, 15.1; Anal. Calc. (%) for $C_{19}H_{21}N_3O_2S_2$ (387.5): C, 58.89; H, 5.46; N, 10.84; Found: C, 58.72; H, 5.35; N, 10.70%.

2.5 *6-Amino-2-(butylthio)pyrimidine-4(3H)-one (**6**)*

Yield 96%; White powder, M.p. 290-292°C; IR (KBr): 3464, 3274, 3194 (N-H),1661 (CONH) cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 11.43 (s, br., 1H, NH), 6.39 (s, br., 2H, NH_2), 4.90 (s, 1H, CH), 3.06 (t, J = 7.4 Hz, 2H, CH_2), 1.59 (quint, J = 7.2 Hz, 2H, CH_2),1.38 (sextet, J = 7.4 Hz, 2H, CH_2), 0.89 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 164.2 (C=O), 163.5, 162.2, 81.2, 30.9, 29.0, 21.3, 13.5.

2.5a *2,8-Bis(butylthio)-5-(2,4-dichlorophenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7a**)*: Yield 96%; White powder, M.p. 310-312°C; IR (KBr): 3352, 3198 (N-H), 1649 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.07 (s, br, 2H, NH), 7.40 (d, J = 2.0 Hz, 1H, Ar-H), 7.32 (dd, J = 8.4, 2.4 Hz, 1H, Ar-H), 7.21 (d, J = 8.4 Hz, 1H, Ar-H), 6.79 (s, br., 1H, NH), 5.39 (s, 1H, CH), 3.11 (m, 4H, 2CH_2), 1.61 (quint., J = 7.2 Hz, 4H, 2CH_2), 1.39 (sextet, J = 7.4 Hz, 4H, 2CH_2), 0.91 (t, J = 7.4 Hz, 6H, 2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 161.5 (C=O),158.2, 151.0, 150.1, 138.0, 133.9, 131.0, 130.6, 129.0, 127.0, 33.0, 24.3, 21.1, 15.1, 12.1; Anal. Calc. (%) for $C_{23}H_{25}Cl_2N_5O_2S_2$ (538.5): C, 51.30; H, 4.68; N, 13.00; Found: C, 51.21; H, 4.54; N, 12.89%.

2.5b *2,8-Bis(butylthio)-5-(3,4-dimethoxyphenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7b**)*: Yield 90%; White powder, M.p. 308-309°C; IR (KBr): 3356, 3179 (N-H),1646 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 11.93 (s, br., 2H, NH), 6.78 (d, J = 8.4 Hz, 1H, Ar-H), 6.60 (d, J = 1.2 Hz, 1H, Ar-H), 6.52 (dd, J = 8.4, 1.2 Hz, 1H, Ar-H), 3.71 (s , 3H, OCH_3), 3.62 (s , 3H, OCH_3), 5.42 (s, 1H, CH), 3.11 (t, J = 7.2 Hz, 4H, 2CH_2), 1.62 (quint., J = 7.2 Hz, 4H, 2CH_2), 1.39 (sextet, J = 7.4 Hz, 4H, 2CH_2), 0.90 (t, J = 7.4 Hz, 6H, 2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6)δ_C: 161.5 (C=O), 157.5, 157.4, 148.2, 146.5, 131.6, 118.3, 111.4, 111.1, 55.4 (OCH_3), 55.3 (OCH_3), 33.0, 30.9, 28.9, 21.3, 13.5; Anal. Calc. (%) for $C_{25}H_{31}N_5O_4S_2$ (529.7): C, 56.69; H, 5.89; N, 13.22; Found: C, 56.57; H, 5.73; N, 13.10%.

2.5c *52,8-Bis(butylthio)-5-(4-boromophenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7c**)*: Yield 93%; White powder, M.p. 314-316°C; IR (KBr): 3342, 3186 (N-H stretch),1657 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 11.98 (s, br., 2H, NH),), 7.34 (d, J = 8.0 Hz, 2H, Ar-H), 6.93 (d, J = 8.0 Hz, 2H, Ar-H), 6.80 (s, br., 1H, NH), 5.38 (s, 1H, CH), 3.08 (m , 4H, 2CH_2), 1.58 (m, 4H, 2CH_2), 1.36 (m, 4H, 2CH_2),0.87 (t, J = 7.2 Hz, 6H, 2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 163.1 (C=O), 160.1, 158.4, 139.3, 130.8, 129.4, 118.6, 92.1, 33.6, 31.3, 29.4, 21.7, 14.0; Anal. Calc. (%) for $C_{23}H_{26}BrN_5O_2S_2$ (548.5): C, 50.36; H, 4.78; N, 12.77; Found: C, 50.19; H, 4.65; N, 12.63%.

2.5d *2,8-Bis(butylthio)-5-(4-nitrophenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7d**)*: Yield 94%; White powder, M.p. 305-307°C; IR (KBr): 3344, 3184 (N-H), 1657 (CONH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.0 (s, br., 2H, NH), 8.09 (d, J = 8.8 Hz, 2H, Ar-H), 7.28 (d, J = 8.8 Hz, 2H, Ar-H), 6.88 (s, br, 1H, NH), 5.55 (s, 1H, CH), 3.05 (m , 4H, 2CH_2), 1.63 (quint., J = 7.2 Hz, 4H, 2CH_2), 1.40 (sextet, J = 7.4 Hz, 4H, 2CH_2), 0.91 (t, J = 7.4 Hz, 6H, 2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 163.1 (C=O), 161.2, 158.0, 148.5, 145.2, 127.9, 122.8, 99.3, 34.0, 30.8, 29.0, 21.3, 13.4; Anal. Calc. (%) for $C_{23}H_{26}N_6O_4S_2$ (514.6): C, 53.68; H, 5.09; N, 16.33; Found: C, 53.55; H, 5.15; N, 16.18%.

2.5e *2,8-Bis(butylthio)-5-(2-hydroxyphenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7e**)*: Yield 95%; White powder, M.p. 312-314°C; IR (KBr): 3454 (O-H stretch), 3454, 3362,1653 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.54 (s, br., 1H, NH), 11.32 (s, br., 1H, NH), 7.15 (m, 1H, Ar-H),7.02 (m, 3H, Ar-H), 5.35 (s, 1H, CH), 3.14 (t , J = 7.2 Hz, 2H, CH_2), 3.07 (t , J = 7.0 Hz, 2H, CH_2), 1.62 (m, 4H, $2CH_2$), 1.39 (m, 4H, $2CH_2$), 0.93 (t, J = 7.4 Hz, 3H, CH_3), 0.91 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 162.2 (C=O), 159.9, 155.8, 150.7, 128.9, 128.1, 127.8, 127.0, 124.6, 124.4, 116.0, 98.4, 96.7, 31.0, 29.4, 25.6, 21.9, 21.8, 14.0, 13.9; Anal. Calc. (%) for $C_{23}H_{27}N_5O_3S_2$ (485.6): C, 56.88; H, 5.60; N, 14.42; Found: C, 56.79; H, 5.51; N, 14.32%.

2.5f *2,8-Bis(butylthio)-5-(3-hydroxyphenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7f**)*: Yield 89%; White powder, M.p. 308-310°C; IR (KBr): 3337 (O-H stretch), 3337, 3180 (N-H stretch), 1659 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 11.94 (s, br., 2H, NH), 9.0 (s,1H, OH), 6.97 (t, J = 8.2 Hz, 1H, Ar-H), 6.74 (s, br., 1H, NH), 6.46 (m, 3H, Ar-H), 5.39 (s, 1H, CH), 3.1 (m , 4H, $2CH_2$), 1.61 (quint., J = 7.2 Hz, 4H, $2CH_2$), 1.38 (sextet, J = 7.4 Hz, 4H, $2CH_2$), 0.9 (t, J = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 163.4 (C=O), 158.0, 157.4, 141.4, 128.8, 117.9, 113.9, 112.3, 92.5, 33.8, 31.4, 29.4, 21.8, 14.0; Anal. Calc. (%) for $C_{23}H_{27}N_5O_3S_2$ (485.6): C, 56.88; H, 5.60; N, 14.42; Found: C, 56.77; H, 5.45; N, 14.35%.

2.5g *2,8-Bis(butylthio)-5-(4-fluorophenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7g**)*: Yield 85%; White powder, M.p. 315-316°C; IR (KBr): 3344, 3188 (N-H stretch), 1651 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H:11.96 (s, br, 2H, NH), 6.98 (m, 4H, Ar-H), 6.8 (s, br, 1H, NH), 5.40 (s, 1H, CH), 3.16 (m , 4H, $2CH_2$), 1.58 (m, 4H, $2CH_2$), 1.36 (m, 4H, $2CH_2$),0.88 (t, J = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 162.1 (C=O), 158.3, 140.8, 128.8, 126.4, 114.7, 112.8, 92.7, 33.6, 31.3, 29.4, 21.8,14.0; Anal. Calc. (%) for $C_{23}H_{26}FN_5O_2S_2$ (487.6): C, 56.65; H, 5.37; N, 14.36; Found: C, 56.48; H, 5.21; N, 14.25%.

2.5h *2,8-Bis(butylthio)-5-(naphthalene-2-yl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7h**)*: Yield 80%; White powder, M.p. 319-320°C; IR (KBr): 3345, 3192 (N-H), 1617 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.00 (s, br., 2H, NH), 7.82 (m, 1H, Ar-H), 7.78 (m, 1H, Ar-H), 7.72 (d, J = 8.8, 1H, Ar-H), 7.43 (d, J = 10.0, 1H, Ar-H), 7.40 (d, J = 4.8, 1H, Ar-H), 7.24 (dd, J = 8.4, 1.2, 1H, Ar-H), 6.80 (s, br, 1H, NH), 5.62 (s, 1H, CH), 3.13 (t, J = 7.2, 4H, $2CH_2$), 1.64 (quint., J = 7.2 Hz, 4H, $2CH_2$), 1.41 (sextet,J = 7.4 Hz, 4H, $2CH_2$), 0.92 (t, J = 7.4 Hz, 6H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 161.6 (C=O), 157.8, 137.2, 133.0, 131.6, 128.6, 127.4, 127.1, 125.5, 124.8, 123.5, 33.7, 30.9, 29.0, 21.3, 13.5; Anal. Calc. (%) for $C_{27}H_{29}N_5O_2S_2$ (519.8): C, 62.40; H, 5.62; N, 13.48; Found: C, 62.23; H, 5.42; N, 13.33%.

2.5i *2,8-Bis(butylthio)-5-(5-methyl-thiophen-2-yl)-5,10-dihydropyrido[2,3-d:5,6-d] dipyrimidine-4,6(3H,7H)-dione (**7i**)*: Yield 87%; White powder, M.p. 317-318°C; IR (KBr): 3341, 3180 (N-H), 1645 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H:12.00 (s, br., 2H, NH), 7.10 (d, J = 8.4 Hz, 1H, Ar-H), 6.94 (d, J = 8.4 Hz, 1H, Ar-H), 6.74 (s, br., 1H, NH), 5.41 (s, 1H, CH), 3.11 (t, J = 7.2, 4H, $2CH_2$), 2.43 (s, 3H, CH_3), 1.62 (quint., J = 7.2 Hz, 4H, $2CH_2$), 1.39 (sextet), J = 7.4 Hz, 4H, $2CH_2$), 0.91 (t, J = 7.4 Hz, 6H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 159.3 (C=O), 157.5, 136.2, 133.6, 127.3, 125.7, 110.0, 33.0, 30.9, 28.9, 21.3, 15.0, 13.5; Anal. Calc. (%) for $C_{22}H_{27}N_5O_2S_3$ (489.7): C, 53.96; H, 5.56; N, 14.30; Found: C, 53.84; H, 5.45; N, 14.12%.

2.5j *2,8-bis(butylthio)-5-(9H-fluorene-2-yl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7j**)*: Yield 92%; White powder, M.p. 318-320°C; IR (KBr): 3347, 3317, 3203 (N-H),1640 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 11.99 (s, br., 2H, NH), 7.80 (d, J = 7.6, 1H, Ar-H), 7.70 (d, J = 8.0, 1H, Ar-H), 7.53 (d, J = 8.8, 1H, Ar-H), 7.43 (d, J = 10.0, 1H, Ar-H), 7.40 (d, J = 4.8, 1H, Ar-H),7.24 (t, J = 7.6, 1H, Ar-H) ,7.26 (m, 1H, Ar-H) 7.05 (d, J = 8.0, 1H, Ar-H), 6.78 (s, br, 1H, NH), 5.56 (s, 1H, CH), 3.82 (s, 2H, CH_2), 3.10 (m, J = 7.2, 4H, $2CH_2$), 1.67 (quint., J = 7.2 Hz, 4H, $2CH_2$), 1.42 (sextet, J = 7.4 Hz, 4H, $2CH_2$), 0.99 (t, J = 7.4 Hz, 6H, $2CH_3$): ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 157.7, 142.8, 142.4, 141.3, 138.4, 126.6, 125.4, 125.0, 123.0, 119.5, 119.2, 36.3, 33.7, 31.1, 29.0, 22.3, 13.2; Anal. Calc. (%)for $C_{28}H_{31}N_5O_2S_2$ (533.7): C, 63.01; H, 5.85; N, 13.12; Found: C, 63.12; H, 5.76; N, 13.01%.

2.5k *2,8-Bis(butylthio)-5-(4-chlorophenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7k**)*: Yield 95%; White powder, M.p. 307-308°C;

IR (KBr): 3344, 3184 (N-H), 1649 (CONH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 11.96 (s, br., 2H, NH), 7.24 (d, J = 8.4 Hz, 2H, Ar-H), 7.02 (d, J = 8.4 Hz, 2H, Ar-H), 6.82 (s, br., 1H, NH), 5.44 (s, 1H, H, CH), 3.11 (m , 4H, $2CH_2$), 1.62 (quint., J = 7.2 Hz, 4H, $2CH_2$), 1.39 (sextet, J = 7.4 Hz, 4H, $2CH_2$),0.91 (t, J = 7.4 Hz, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 163.8 (C=O), 161.9, 158.3, 138.8, 129.8, 129.0, 128.0, 92.7, 33.5, 24.3, 20.5, 15.2,13.1 ; Anal. Calc. (%) for $C_{23}H_{26}ClN_5O_2S_2$ (504.1): C, 54.80; H, 5.20; N, 13.89; Found: C, 54.71; H, 5.08; N, 13.72%.

2.5l *2,8-bis(butylthio)-5-(2-Hydroxy-5-((4-nitrophenyl)diazenyl)phenyl)-5,10-dihydropyrido[2,3-d:5,6-d] di-pyrimidine-4,6(3H,7H)-dione (**7l**)*: Yield 87%; White powder, M.p. 310-312°C; IR (KBr): 3448 (O-H stretch), 3366, 3166 (N-H stretch), 1645 (CONH), 1533, 1340 (NO_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.68 (s, br., 1H, NH),11.93 (s, br., 1H, NH), 9.20 (s, 1H, OH), 8.37 (d, J = 8.4 Hz, 2H, Ar-H),8.01 (d, J = 8.4 Hz, 2H, Ar-H), 7.80 (d, J = 8.8 Hz, 1H, Ar-H), 7.68 (s, 1H, Ar-H), 7.28 (d, J = 8.8 Hz, 1H, Ar-H), 6.24 (s, 1H, NH), 5.2 (s, 1H, CH), 3.15-3.07 (m, 4H, $2CH_2$), 1.70-1.57 (m, 4H, $2CH_2$), 1.43-1.35 (m, 4H, $2CH_2$), 0.95-0.82 (m, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C:164.2 (C=O), 155.6, 154.2, 150.3, 148.7, 130.0, 128.9, 128.4, 126.1, 125.4, 124.5, 124.0, 123.3, 123.0, 120.1, 117.4, 107.4, 106.2, 31.4, 27.9, 23.8, 21.9, 21.8, 14.0; Anal. Calc. (%) for $C_{29}H_{30}N_8O_5S_2$ (634.7): C, 54.88; H, 4.76; N, 17.65; Found: C, 54.96; H, 4.85; N, 17.52%.

2.5m *2,8-Bis(butylthio)-5-(2-hydroxy-5-((2-methyl-4-nitrophenyl)diazenyl)phenyl)-5,10-dihydropyrido[2,3-d:5,6-d]dipyrimidine-4,6(3H,7H)-dione (**7m**)*: Yield 84%; White powder, M.p. 305-307°C; IR (KBr): 3445 (O-H stretch), 3445, 3391 (N-H stretch), 1645 (CONH), 1524, 1340 (NO_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.74 (s, br., 2H, NH),11.53 (s, br., 1H, OH), 8.29 (s, 1H, Ar-H), 8.12 (m, 1H, Ar-H), 7.87 (m, 1H, Ar-H), 7.76-7.60 (m, 2H, Ar-H), 7.36-7.25 (m, 1H, Ar-H), 6.85 (s, br., 1H, NH), 5.2 (s, 1H, CH), 3.18-3.05 (m, 4H, $2CH_2$), 2.73 (s, 3H, CH_3), 1.68-1.56 (m, 4H, $2CH_2$), 1.45-1.35 (m, 4H,$2CH_2$),0.95-0.86 (m, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 161.6 (C=O),154.0, 153.7, 153.3, 152.0, 149.3, 149.2, 148.5, 139.2, 138.9, 125.9, 125.1, 123.2, 122.6, 122.5, 121.5, 118.3, 117.3, 117.0, 113.4, 31.4, 29.9, 29.8, 29.4, 22.0, 21.8, 17.5, 14.0, 13.9; Anal. Calc. (%) for $C_{30}H_{32}N_8O_5S_2$ (648.8): C, 55.54; H, 4.97; N, 17.27; Found: C, 55.33; H, 4.81; N, 17.11%.

2.5n *2,8-Bis(butylthio)-5-(2-hydroxy-5-((2-chlorophenyl)diazenyl)phenyl)-5,10-dihydropyrido[2,3-d:5,6-d] dipyrimidine-4,6(3H,7H)-dione (**7n**)*: Yield 87%; White powder, M.p. 320-321°C; IR (KBr): 3421 (O-H stretch), 3313, 3209 (N-H stretch), 1641 (CONH),1533, 1340 (NO_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ_H: 12.82 (s, br., 2H, NH), 8.24 (s, 1H, OH), 7.88 (d, J = 8.8 Hz, 1H, Ar-H),7.81 (dd, J = 8.8, 2.4 Hz, 1H, Ar-H), 7.76-7.46 (m, 4H, Ar-H), 7.36 (d, J = 8.4 Hz, 1H, Ar-H), 7.32 (s, 1H, NH), 5.15 (s, 1H, CH), 3.16-3.05 (m, 4H, $2CH_2$), 1.69-1.58 (m, 4H, $2CH_2$), 1.46-1.36 (m, 4H, $2CH_2$),0.96-0.92 (m, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 162.21 (C=O), 160.1, 153.1, 149.2, 148.3, 134.3, 133.1, 131.2, 131.1, 130.3, 128.6, 125.8, 124.9, 122.8, 121.6, 118.4, 118.2, 118.0, 117.9, 92.1, 31.0, 29.5, 25.2, 21.8, 21.7, 14.0; Anal. Calc. (%) for $C_{29}H_{30}ClN_7O_3S_2$ (624.2): C, 55.80; H, 4.84; N, 15.71; Found: C, 55.67; H, 4.63; N, 15.62%.

3. Results and Discussion

In recent years, several methods have been reported for the preparation of pyrimido[4,5-*b*]quinolines[27–30] and pyrido[2,3-*d*:6,5-*d*′]dipyrimidines[31–33] using 6-aminouracil or 6-aminothiouracil. Despite this, the search for simple, general and efficient procedures for the preparation of these important heterocyclic compounds is still demanding. In continuation of our research devoted to the development of new benign methodologies in the synthesis of biologically important heterocycles,[34–40] and exploiting valuable catalytic properties of magnetic nanoparticles.[3,7–10] we were interested in the synthesis of novel derivatives of pyrimido[4,5−*b*]quinolines and pyrido[2,3-*d*:6,5-*d*′]dipyrimidines using [γ-Fe_2O_3@HAp-SO_3H] as nanocatalyst.

The magnetic nanoparticles (γ-Fe_2O_3) were synthesized by a chemical co-precipitation technique using ferric and ferrous ions. Based on the report,[7,8] after coating a layer of hydroxyapatite on the surface of the γ-Fe_2O_3 nanoparticles, functionalization with a sulfonic acid group was achieved by treatment with chlorosulfonic acid (0.9 mmol g^{-1} -SO_3H loading) to furnish [γ-Fe_2O_3@HAp-SO_3H.] nanocrystallites. The catalyst was characterized by IR, SEM and XRD. SEM analysis of the catalyst clearly showed the nanosize (33-47 nm) of the particles. In the IR spectrum, the S=O group appeared at 1380 cm^{-1} and surface phosphate groups in the hydroxyapatite cover, overlapped with S–O stretching peak at 560 and 600 cm^{-1}. Hydroxyapatite has received significant regard as one of the most ideal biocompatible materials for encapsulated

iron oxide NPs. This class of materials has reliable chemical stability, biocompatibility and versatility in surface modification.

At the outset of this study, the requisite starting materials (**1, 6**) were prepared by the condensation of thiourea with ethyl cyanoacetate in sodium ethoxide and alkylated by alkyl halide according to the known procedure.[41]

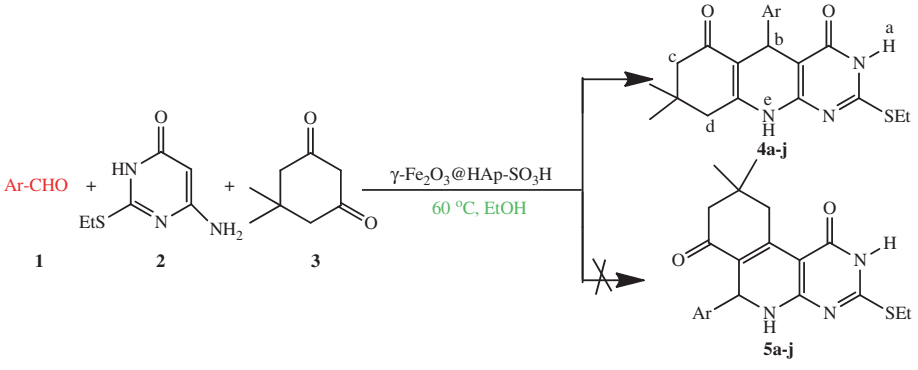
To optimize the desired reaction conditions, one-pot three-component reaction of 6-amino-2-ethylthio pyrimidin-4(3*H*)-one (1 mmol), dimedone (1 mmol) and 2,4-dichlorobenzaldehyde (1 mmol) in the presence of [γ-Fe_2O_3@HAp-SO_3H] (0.01 g) in EtOH (1 mL) was used as the model system. The reaction mixture was heated at 60°C, which produced the product **4a** in 4 min and 94% yield. The effect of various solvents (EtOH, CH_3CN, 1,4-dioxane, CH_2Cl_2 and DMF) and temperatures on the reaction time and the yield was examined. EtOH proved to be the solvent of choice at 60°C. The use of various common acid catalysts such as *P*-TSA, L-proline, $ZnCl_2$, $FeCl_3$, K10, alum, and [bdmim][PF_6] gave the products in lower yields with much longer reaction times compared to the present nanocatalyst.

The reaction between aryl aldehydes (**1**), 6-amino-2-ethylthiopyrimidin-4(3*H*)-one (**2**) and dimedone (**3**) under optimized conditions, gave regiospecifically the linear products (**4a-j**) (scheme 1) in short reaction times and excellent yields (table 1). ^{1}H-NMR of the products showed one proton at $\delta = 4.88$-5.23 ppm for the pyrimidine H_b and one signal at $\delta = 9.77$-9.90 ppm for the NH (H_e) proton, vouching formation of the structures **4a-j** (scheme 1). In this reaction no trace of the angular regioisomer (**5a-j**) was observed.

A plausible mechanism for the formation of **4a-j** is presented in scheme 2, which proceeds through a Knovenagel condensation of aryl aldehyde (**1**) and dimedone (**3**) followed by Michael addition of enamine (**2**) furnishing the desired products.

Encouraged by these results, the application of [γ-Fe_2O_3@HAp-SO_3H] was extended to the preparation of novel pyrido[2,3-*d*:6,5-*d′*]dipyrimidine derivatives (**7a-n**) (scheme 3). The reaction of various arylaldehydes (1 mmol) and butylthiopyrimidin-4(3*H*)-one (2 mmol) (**6**) in the presence of [γ-Fe_2O_3@HAp-SO_3H] (0.02 g) was also investigated and the results are presented in table 2. In this reaction the use of diazenylarylaldehydes (figure 1) which were conveniently prepared by adopting the literature report,[42] furnishing the desired pyrido[2,3-*d*:6,5-*d′*]dipyrimidine derivatives also in high yields (Entries 7i-n). In addition, the efficiency of other acid catalysts including AcOH, *P*-TSA, L-proline, K10, alum, Zns, $FeCl_3$, $ZnCl_2$ and [bdmim][PF_6] was examined for the present conversion and they were less effective (60-120 min) compared to [γ-Fe_2O_3@HAp-SO_3H]. The synthesis of **7a-n** proceeds by catalytic activation of aryl aldehyde (**1**) as in scheme 2, followed by two successive Michael addition of butylthiopyrimidin-4(3*H*)-one (2 mmol) (**6**) and elimination of ammonia.

Recently, the application of ultrasound as a clean and green source of energy in organic synthesis has been increasing. Our recent findings have shown that the synthesis of heterocyclic compounds could be facilitated under ultrasonic irradiations due to its advantages such as mild condition, shorter reaction times and higher yields in comparison with the classical methods.[38,39,43] Therefore, it was decided to examine the effect of ultrasonic irradiation, as an alternative method, on the synthesis of pyrimido[4,5−*b*]quinolines (**4a-j**) and pyrido[2,3-*d*:6,5-*d′*]dipyrimidines (**7a-n**) and compare the results with the present nanaocatalysis. An equimolar mixture of reactants **1**, **2** and **3** and L-proline (3 mol%) in ethanol (1 mL) were placed in a Pyrex-glass open vessel and irradiated at 80°C by ultrasonic irradiation (40 kHz) which furnished the desired products (**4a-j**) in high yields (table 1). This method was also applied to the preparation of pyridodipyrimidines

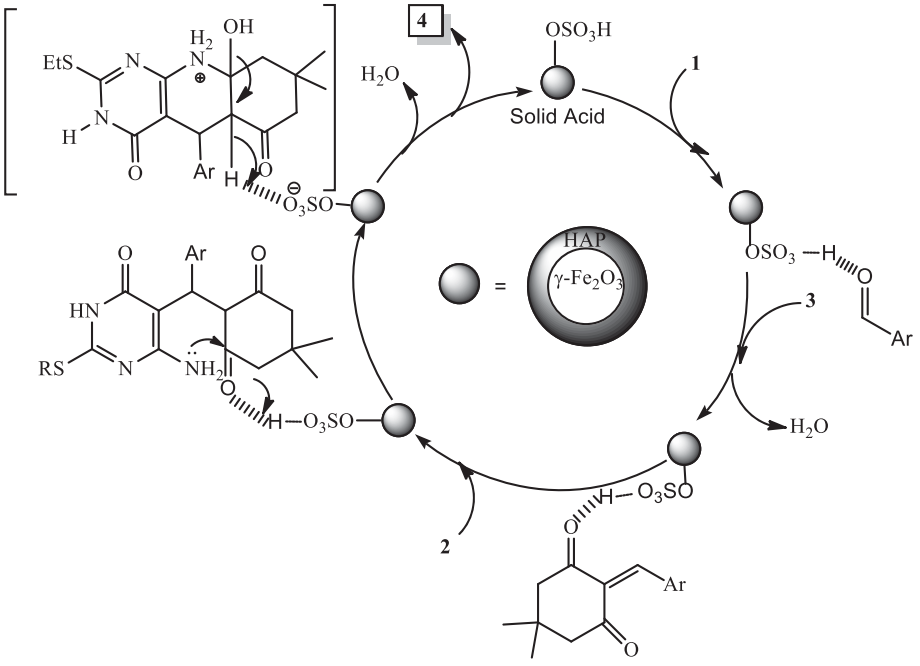


Scheme 1. Synthesis of pyrimido[4,5−*b*]quinolines derivatives (**4a-j**).

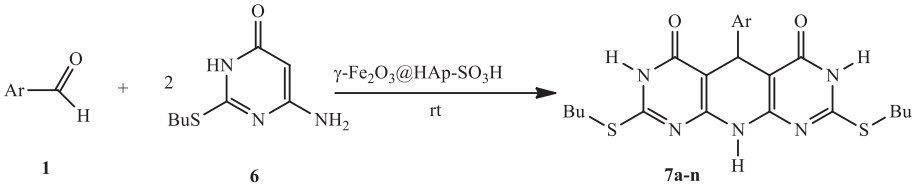
Table 1. One-pot synthesis of pyrimido[4,5−*b*]quinolines derivatives (**4a-j**) in the presence of [γ-Fe_2O_3@HAp-SO_3H] as nanocatalyst (0.01 g) at 60°C, and ultrasonic method.

Entry	Ar	nanocatalyst		Ultrasonic irradiation[b]	
		Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
4a	2,4-$Cl_2C_6H_3$	4	94	7 (7)[c]	87 (83)[c]
4b	2-ClC_6H_4	8	95	13	84
4c	4-ClC_6H_3	6	95	10	85
4d	3-ClC_6H_4	5	91	9	84
4e	4-$O_2NC_6H_4$	6	85	10	77
4f	4-BrC_6H_4	10	84	15	75
4g	2-FC_6H_4	10	92	15	80
4h	4-FC_6H_4	5	92	10	79
4i	C_6H_5	6	89	12	81
4j	2-thienyl	12	95	20	89

[a] Isolated yields. [b] L-proline (3 mol%) in ethanol (1 mL) at 80°C. [c][γ-Fe_2O_3@HAp-SO_3H] (0.01 g/mmol substrate), 80°C.



Scheme 2. A plausible mechanism for the synthesis of **4a-j**.



Scheme 3. Synthesis of pyrido[2,3-*d*:6,5-*d′*]dipyrimidines derivatives (**7a-n**).

7a-n (DMF/AcOH, 80°C) and the results are presented in table 2. A comparison with classical conditions (DMF/AcOH, 120°C) has also been made in table 2. In both cases the ultrasonic method was preferred over

Table 2. One-pot synthesis of pyrido[2,3-d:6,5-d′]dipyrimidines derivatives (**7a-n**) in the presence of [γ-Fe_2O_3@HAp-SO_3H] as nanocatalyst (0.02 g) at r.t, classical (AcOH/DMF 1:1) and ultrasonic methods.

Entry	Ar	nanocatalyst		Classical[b]		Ultrasonic[c]	
		Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
7a	2,4-$Cl_2C_6H_3$	1	96	100	84	10	88
7b	3,4-$(MeO)_2C_6H_3$	1	90	110	80	10	84
7c	4-BrC_6H_4	2	93	110	72	13	82
7d	4-$O_2NC_6H_4$	2	94	120	74	15	85
7e	2-HOC_6H_4	3	95	135	78	17	88
7f	3-HOC_6H_4	1	89	120	80	15	84
7g	4-FC_6H_4	2	85	135	82	14	84
7h	1-hydroxy-2-naphthyl	3	80	140	79	20	80
7i	5-CH_3-2-thienyl	2	87	115	78	15	85
7j	2-(9H-fluorenyl)	1	92	100	90	10	90
7k	4-ClC_6H_4	1	95	140	85	10	87
7l	**A**[d]	2	87	180	78	23	85
7m	**B**[d]	3	84	170	75	20	80
7n	**C**[d]	3	87	175	76	25	82

[a] Isolated yields. [b]AcOH/DMF (1:1) at 120 °C. [c]AcOH/DMF (1:1) at 80°C, [d]2-hydroxy-5-((aryl)diazenyl)phenyl (figure 1).

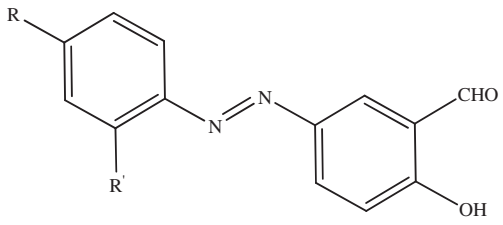


Figure 1. 2-hydroxy-5-(aryldiazenyl)benzaldehyde: **A** (R = NO_2, R′ = H), **B** (R = NO_2, R′ = CH_3), **C** (R = H, R′ = Cl).

the classical method. But the best results in terms of reaction time, temperature and yield were obtained by the use of nanocatalyst [γ-Fe_2O_3@HAp-SO_3H] (tables 1 and 2).

We have also checked the reusability of the catalyst in above mentioned reactions by using the preparation of **4a** and **7a** as model reactions. After completion of the reaction, the nanocatalyst was separated from the reaction medium simply by an external magnetic field, washed with ethanol, dried under vacuum and reused for the next run. After 4 successive runs in each reaction, the catalytic activity of [γ-Fe_2O_3@HAp-SO_3H] was almost remained unchanged. The products were fully characterized through their spectral (IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses. In some of the pyridodipyrimidine products the symmetry is distorted by introducing large (aryldiazenyl)phenyl substituent at C-5 position. This is evident from the ^{13}C NMR data of compounds **7l-n** and ^{1}H NMR of **7l** (two separate NH at 12.68 and 11.93 ppm).

4. Conclusions

In the development of green chemistry procedures and suitable methods for the synthesis of biologically important compounds, we report here a novel method for the three-component synthesis of pyrimido [4,5−*b*]quinolines and pyrido[2,3-*d*:6,5-*d′*]dipyrimidines using [γ-Fe_2O_3@HAp-SO_3H] as recyclable nanocatalyst. The reaction induced by the nanocatalyst offered better yields, shorter reaction times and lower temperatures than other methods described here. This protocol involves mild reaction conditions, a green and cost-effective catalyst, an easy work-up procedure and avoids the use of large volumes of hazardous organic solvents which makes it a useful alternative to previously applied procedures. Also, the magnetic nature of these nanoparticles allows for easy recovery and recycling of the catalysts by an external magnetic field.

Acknowledgement

The authors are grateful to the Research Council of University of Guilan for the financial support of this research work.

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