Synthesis of new sulfanyl pyrimidin-4(3H)-one and ethyl-2-(pyridin-4yl) methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives under conventional and heterogeneous conditions

Fatma A. Bassyouni[a], Omar A. Fathalla[b]

[a]Chemistry of Natural and Microbial Products Department and Pharmaceutical Research Group, Center of Excellence for Advanced Sciences, National Research Centre, [b]Department of Medicinal Chemistry, National Research Centre, Cairo, Egypt

Correspondence to Fatma Bassyouni, PhD, Chemistry of Natural and Microbial Products Department and Pharmaceutical Research Group, Center of Excellence for Advanced Sciences, National Research Centre, 12311 Cairo, Egypt
Tel: +20 111 859 6967; fax: +20 233 370 931
e-mail: fatma.nrc@hotmail.com

Received 9 May 2013
Accepted 18 August 2013

Egyptian Pharmaceutical Journal
2013, 12:186–192

Background and objectives
Heterocyclic systems with a pyrimidine nucleus display a wide spectrum of biological activities, such as antimicrobial, antiviral, anticancer, antidepressive, anti-inflammatory, antitubercular, diuretic, and anticoagulant. The aim of the present study was the synthesis of new heterocyclic sulfanylpyrimidin-4(3H)-one derivatives by adopting simple and efficient methods, in addition to ethyl-2-(pyridin-4-yl) methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives in excellent yields.

Materials and methods
The synthesis of the titled sulfanyl pyrimidin-4(3H)-one derivatives was achieved by the reaction of compounds 1a–c with phenacyl bromide, 4-methyl phenacyl bromide, or 4-nitrophenacyl bromide to give 5-(morpholin-4-ylmethyl)-2-oxoethylphenyl-sulfanyl-pyrimidin-4(3H)-ones (2a–c), [(4-methylpiperazin-1-yl) methyl]-2-oxoethylphenyl-sulfanyl-pyrimidin-4(3H)-ones (3a–c), or piperidin–1–yl) methyl]sulfanyl-pyrimidin-4(3H)-ones (4a–c), respectively. In addition, several heterocyclic pyrimidine derivatives such as ethyl-2-((pyridin-4-yl)methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives 6a–h were prepared by the reaction of 1,2 dihydropyrimidone derivatives 5a–h with picolyl chloride using conventional and heterogeneous catalysts such as silica sulfuric acid and CuY-Zeolite. The structures of the synthesized compounds were confirmed by elemental analyses and spectroscopic methods.

Results and conclusion
A simple and efficient method was used for the synthesis of sulfanyl pyrimidin-4(3H)-one derivatives through reaction with different reagents. Also, ethyl-2-((pyridin-4-yl)methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives were obtained using conventional and heterogeneous conditions in excellent yields.

Keywords:
dihydropyrimidines, heterogeneous catalyst, pyrimidines, sulfany pyrimidines, synthesis

Egypt Pharm J 12:186–192

1687-4315

Introduction

Since many decades, bioactive heterocyclic compounds have been one of the main topics of interest among medicinal chemists as it displays a number of pharmacological activities. These compounds are used as a starting point to prepare complex heterocyclic scaffolds with numerous pharmacological properties [1,2]. Pyrimidine derivatives form a component in a number of useful drugs such as nifedipine for the treatment of cardiovascular diseases, fluorouracil and monastrol for treatment of cancer, flucytosine as antimycotic, and bosentan for the treatment of pulmonary artery hypertension [3]. Moreover, several pyrimidine derivatives are associated with many biological activities such as antitumoral [4], anti-HIV-1 [5], analgesic [6], antidepressive [7], anticonvulsant [8], antimicrobial [9], herbicidal [10], anti-inflammatory, antioxidant [11,12], in-vitro COX-1 and COX-2 inhibition activity [13], antitubercular [14], and diuretic [15]. In addition, pyrimidine compounds are also used as hypnotic drugs for the nervous system [16], for calcium-sensing receptor antagonists [17], and for antagonists of the human A2A adenosine receptor [18]. Furthermore, the synthesis and chemistry of sulfanyl pyrimidines have recently been reported by a vast number of papers for the synthesis of different biological activities such as anti-HIV and antimicrobial, and as a new class of antifilarial agents [19–22].

In view of these points and as a part of our research interest in heterocyclic pyrimidine derivatives, this work involves the development of new methods for the synthesis of heterocyclic sulfanyl pyrimidin-4(3H)-one derivatives and ethyl-2-((pyridin-4-yl)methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives under conventional and heterogeneous conditions.

Experimental

Chemistry

Melting points were determined in open capillary tubes on an Electro thermal digital melting point apparatus (SMP30; Stuart, StaffordShire, ST150SA, UK) and reported uncorrected. IR spectra were recorded on a Jasco FT/IR Fourier transform infrared spectrophotometer

(South san Francisco, CA 94080, USA) using KBr discs.[1]H-NMR spectra were determined on a JEOL 500 MHz spectrometer (Tokyo, Japan) in DMSO-d_6 using TMS as the internal reference. Mass spectra were recorded on mass spectrometer JEOL (Japan) at 70 eV. Elemental analyses were performed at the Micro analytical Laboratory, Cairo University, and the results were found to be in agreement (±0.4%) with the calculated values. Purity of the synthesized compounds was checked by thin-layer chromatography (TLC) silica-gel alumina sheet-Merck 60-F254 precoated sheets (Merck, Darmstadt, Germany).

Synthesis of 2-thioxo-2,3-dihydropyrimidin-4 (1H)-one derivatives (1a–c) [23]

A mixture of paraformaldehyde (0.005 mol), mopholine or *N*-methylpiprazine or pipridine (0.005 mol) in absolute ethanol (25 ml) was heated under reflux with stirring for 1 h, followed by addition of (0.005 mol) 2-thiouracil in absolute ethanol (25 ml). The reaction mixture was then refluxed with stirring for 8–10 h. The progress of the reaction was monitored by TLC (eluent: chloroform–methanol 3 : 1). After cooling, the precipitated solid product was collected by filtration, washed with water, dried under vacuum, and crystallized from absolute ethanol to give compounds 1a–c. Compounds 1a–c were synthesized as reported in the literature [23]. Their molecular structure and purity were confirmed by spectroscopic analysis.

General procedure for the synthesis of 5-(morpholin-4-ylmethyl)-2-oxoethylphenyl-sulfanyl pyrimidin–4 (3H)-one derivatives (2a–c)

Sodium metal (1 g) was dissolved in absolute ethanol (50 ml) and left to cool to room temperature. Thereafter, sodium ethoxide solution (15 ml) was added to compound 1a (0.01 mol) and then phenacyl bromide or 4-methyl phenacyl bromide or 4-nitrophenacyl bromide (0.01 mol) was added dropwise and heated under reflux with stirring for 5–6 h. During the procedure the reaction progress was monitored by TLC (eluent: chloroform–methanol 3 : 1). The products were neutralized, and the precipitated solid was filtered, washed several times with ice water, dried under vacuum, and crystallized from 95% acetic acid to afford compounds 2a–c.

5-(Morpholin-4-yl-methyl)-2-[(2-oxo-2-phenylethyl)sulfanyl]pyrimidin-4(3H)-one (2a), 69% yield, m.p.>300°C. Anal. calcd. for $C_{17}H_{19}N_3O_3S$ (345.41): C, 59.41; H, 5.54; N, 12.17. Found: C, 59.38; H, 5.51; N, 12.11. IR (KBr, cm^{-1}): 3350 (NH), 3160 (CH-aromatic), 2970 (CH-aliphatic), 1675, 1680 (2C=O), 1629 (C=C), 1270 (C=S of thiouracil). [1]H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.10–2.30 (4H, m, CH_2–N–CH_2), 3.60–3.79 (4H, m, CH_2–O–CH_2), 4.30 (2H, s, CH_2), 4.45 (2H, s, CH_2), 7.10–7.40 (4H, m, CH-aromatic), 8.10 (1H, s, CH-thiouracil), 10.20 (1H, s, NH exchangeable with D_2O).

2-{[2-(4-Methylphenyl)-2-oxoethyl]sulfanyl}-5-(morpholin-4-ylmethyl)pyrimidin-4(3H)-one (2b), 67% yield, m.p. 267–269°C. Anal. calcd. for $C_{18}H_{21}N_3O_3S$ (359.44): C, 60.15; H, 5.89; N, 11.69. Found: C, 60.10; H, 5.83; N, 11.65. IR (KBr, cm^{-1}): 3340 (NH), 3174 (CH-aromatic), 2960 (CH-aliphatic), 1678, 1685 (2C=O), 1630 (C=C), 1275 (C=S of thiouracil). [1]H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.00 (3H, s, CH_3), 2.15–2.30 (4H, m, CH_2-N-CH_2), 3.35-3.45 (4H, m, CH_2-O–CH_2), 4.35 (2H, s, CH_2), 4.50 (2H, s,CH_2), 7.25–7.55 (4H, m, CH-aromatic), 8.20 (1H, s, CH-thiouracil), 10.00 (1H, s, NH exchangeable with D_2O).

5-(Morpholin-4-ylmethyl)-2-{[2-(4-nitrophenyl)-2-oxoethyl]sulfanyl}pyrimidin-4(3H)-one (2c), 74% yield, m.p. 245–247°C. Anal. calcd. for $C_{17}H_{18}N_4O_4S$ (390.41): C, 52.30; H, 4.65; N, 14.35. Found: C, 52.26; H, 4.59; N, 14.31. IR (KBr, cm^{-1}): 3342 (NH), 3274 (CH-aromatic), 2968 (CH-aliphatic), 1670, 1680 (2C=O), 1636 (C=C), 1278 (C=S of thiouracil). [1]H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.20–2.40 (4H, m, CH_2-N-CH_2), 3.50–3.65 (4H, m, CH_2-O-CH_2), 4.25 (2H, s, CH_2), 4.45 (2H, s, CH_2), 7.30–7.50 (4H, m, CH-aromatic), 8.25 (1H, s, CH-thiouracil), 10.40 (1H, s, NH exchangeable with D_2O).

General procedure for the synthesis of 5-[(4-methylpiperazin-1-yl)methyl]-2-oxoethylphenyl-sulfanyl-pyrimidin-4(3H)-one derivatives (3a–c)

These compounds were synthesized using the same procedure as described for synthesis of compounds 2a–c by using compound 1b with phenacyl bromide, 4–methyl phenacyl bromide, or 4-nitrophenacyl bromide to give compounds 3a–c, respectively.

5-[(4-Methylpiperazin-1-yl)methyl]-2-[(2-oxo-2-phenylethyl)sulfanyl]pyrimidin-4(3H)-one (3a), 67% yield, m.p. 285–287°C. Anal. calcd. for $C_{18}H_{22}N_4O_2S$ (358.46): C, 60.31; H, 6.19; N, 15.63. Found: C, 60.25; H, 6.16; N, 15.57. IR (KBr, cm^{-1}): 3345 (NH), 3167 (CH-aromatic), 2972 (CH-aliphatic), 1679, 1689 (2C=O),1630 (C=C), 1274 (C=S of thiouracil). [1]H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.30 (3H, s, N-CH_3), 2.60–2.80 (4H, m, CH_2-N-CH_2), 3.60–3.78

(4H, m, CH_2-N-CH_2), 4.40 (2H, s,CH_2), 4.55 (2H, s, CH_2), 7.30-7.55 (5H, m, CH-aromatic), 8.15 (1H, s, CH-thiouracil), 10.10 (1H, s, NH exchangeable with D_2O).

2-{[2-(4-Methylphenyl)-2-oxoethyl]-sulfanyl}-5-[(4-methylpiperazin-1-yl)methyl]pyrimidin-4(3H)-one (3b), 72% yield, m.p. 235–237°C. Anal. calcd. for $C_{19}H_{24}N_4O_2S$ (372.48): C, 61.27; H, 6.49; N, 15.04. Found: C, 61.23; H, 6.46; N, 15.00. IR (KBr, cm^{-1}): 3340 (NH), 3174 (CH-aromatic), 2960 (CH-aliphatic), 1670, 1680 (2C=O), 1635 (C=C), 1275 (C=S of thiouracil). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.10 (3H, s, CH_3), 2.35 (3H, s, N-CH_3), 2.60-2.85 (4H, m, CH_2-N-CH_2), 3.65-3.80 (4H, m, CH_2-N-CH_2), 4.30 (2H, s, CH_2), 4.50 (2H, s, CH_2), 7.15-7.45 (4H, m, CH-aromatic), 8.20 (1H, s, CH-thiouracil), 9.95 (1H, s, NH exchangeable with D_2O).

5-[(4-Methylpiperazin-1-yl)methyl]-2-{[2-(4-nitrophenyl)-2-oxoethyl]sulfanyl}pyrimidin-4(3H)-one (3c), 70% yield, m.p. 215–217°C. Anal. calcd. for $C_{18}H_{21}N_5O_4S$ (403.46): C, 53.59; H, 5.25; N, 17.36. Found: C, 53.56; H, 5.20; N, 17.30. IR (KBr, cm^{-1}): 3350 (NH), 3260 (CH-aromatic), 2955 (CH-aliphatic), 1675, 1680 (2C=O), 1638 (C=C), 1270 (C=S of thiouracil). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.30 (3H, s, N-CH_3), 2.40–2.55 (4H, m, CH_2-N–CH_2), 3.65–3.85 (4H, m, CH_2–N-CH_2), 4.35 (2H, s, CH_2), 4.55 (2H, s, CH_2), 7.10–7.40 (4H, m, CH-aromatic), 8.16 (1H, s, CH-thiouracil), 10.25 (1H, s, NH exchangeable with D_2O).

General procedure for the synthesis of 5-[(piperidin-1–yl) methyl]sulfanyl-pyrimidin-4(3H)-one derivatives (4a–c)

These compounds were synthesized using the same procedure as that described for synthesis of compounds 2a–c by using compound 1c with phenacyl bromide, 4-methyl phenacyl bromide, or 4-nitrophenacyl bromide to give compounds 4a–c, respectively.

2-[(2-Oxo-2-phenylethyl) sulfanyl]-5-(piperidin-1-yl)methyl)]pyrimidin-4(3H)-one (4a), 68% yield, m.p. 274–276°C. Anal. calcd. for $C_{18}H_{21}N_3O_2S$ (343.44): C, 62.95; H, 6.16; N, 12.23. Found: C, 62.90; H, 6.13; N, 12.19. IR (KBr, cm^{-1}): 3355 (NH), 3160 (CH-aromatic), 2970 (CH-aliphatic), 1675, 1680 (2C=O), 1628 (C=C), 1279 (C=S of thiouracil). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.15–2.35 (4H, m, CH_2-N–CH_2), 3.60–3.90 (4H, m, 2CH_2), 4.28 (2H, s, CH_2), 4.40 (2H, s, CH_2), 4.55 (2H, s, CH_2), 7.10–7.45 (4H, m, CH-aromatic), 8.26 (1H, s, CH-thiouracil), 9.85 (1H, s, NH exchangeable with D_2O).

2-{[2-(4-Methylphenyl)-2-oxoethyl]sulfanyl}-5-(piperidin-1-yl)methyl]pyrimidin-4(3H)-one (4b), 71% yield, m.p. 215–217°C. Anal. calcd. for $C_{19}H_{23}N_3O_2S$ (357.47): C, 63.49; H, 6.49; N, 11.75. Found: C, 63.43; H, 6.45; N, 11.70. IR (KBr, cm^{-1}): 3340 (NH), 3174 (CH-aromatic), 2960 (CH-aliphatic) 1670, 1680 (2C=O), 1635 (C=C), 1270 (C=S of thiouracil). ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 2.15 (3H, s, CH_3), 2.30–2.45 (4H, m, CH_2-N-CH_2),), 3.55–3.80 (4H, m, 2CH_2), 4.20 (2H, s, CH_2), 4.35 (2H, s, CH_2), 4.50 (2H, s, CH_2), 7.20–7.50 (4H, m, CH-aromatic), 8.22 (1H, s, CH-thiouracil), 10.20 (1H, s, NH exchangeable with D_2O).

2–{[2–(4–Nitrophenyl)–2–oxoethyl]sulfanyl}–5-(piperidin–1-yl)methyl]pyrimidin-4(3H)-one (4c), 68% yield, dark brown crystals m.p. 145–147°C. Anal. calcd. for $C_{18}H_{20}N_4O_4S$ (388.44): C, 55.66; H, 5.19; N, 14.42. Found: C, 53.62; H, 5.14; N, 14.36. IR (KBr, cm^{-1}): 3348 (NH), 3174 (CH-aromatic), 2966 (CH-aliphatic), 1679, 1685 (2C=O), 1630 (C=C), 1268 (C=S of thiouracil). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.36 (4H, m, CH_2-N-CH_2), 3.60–3.80 (4H, m, 2CH_2), 4.20 (2H, s,CH_2), 4.45 (2H, s, CH_2), 4.55 (2H, s, CH_2), 7.20–7.45 (4H, m, CH-aromatic), 8.16 (1H, s, CH-thiouracil), 9.90 (1H, s, NH exchangeable with D_2O).

General procedure for the synthesis of 1,2 dihydropyrimidone derivatives (5a–h)

Method A

A mixture of urea or thiourea (1 mmol), benzaldehyde derivatives such as 4-flourobenzaldehyde, 4-chlorobenzaldehyde, 2-thiophene aldehyde, or 2-furfuraldehyde (1 mmol), and ketoester (1.1 mmol), silica sulfuric acid (SSA; 0.06 g equal to 0.15 mmol), silica gel (0.06 g), and *P*-toluenesulfonic acid (0.06 g) in ethanol (25 ml) was stirred at 100°C for 3–5 h. After completion of the reaction, which was confirmed by TLC (eluent: *n*-hexane/ethyl acetate: 2 : 1), hot ethanol (20 ml) was added to the residue, which was then filtered. The resulting solution was condensed under reduced pressure. Finally, the precipitate product was recrystallized from ethanol to give compounds 5a–h in excellent yields of 86–885%.

Method B

A mixture of urea or thiourea (0.5 mmol), benzaldehyde derivatives such as 4-flourobenzaldehyde, 4-chlorobenzaldehyde, 2-thiophene aldehyde, or 2-furfuraldehyde (0.5 mmol), and ketoester (0.55 mmol) in ethanol (20 ml) and nano-CuY-Zeolite (0.005 g) was stirred at room temperature for 2–3 h. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate: 2/1). After completion of the reaction, the used catalyst was collected by filtration using cold water (20 ml) to produce the products and then washed with water/ethanol (70 : 30). The solvent was evaporated

under vacuum, and the product was recrystallized from absolute ethanol to form compounds 5a–h in excellent yields of 88–90%.

General procedure for the synthesis of compounds ethyl–2-((pyridin-4-yl)methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives (6a–h)

Method C

A mixture of compounds 5a–h (0.1 mmol) and potassium carbonate (0.138 g, 1 mmol) in DMF (5 ml) and picolyl chloride (0.1 mmol) was stirred at room temperature for 7–8 h. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate: 2/1). The solvent was removed under vacuum, and the products were washed with ice water (25 ml). The precipitated product was filtered and dried and then recrystallized from ethanol to form compounds 6a–h in yields of 74–77%.

Method D

A mixture of compounds 5a–h (0.1 mmol), picolyl chloride (0.1 mmol), and SSA (0.1 g) in 20 ml ethanol was stirred at 110°C for 3–5 h. After completion of the reaction, which was confirmed by TLC (eluent: *n*-hexane/ethyl acetate: 2/1), hot ethanol (20 ml) was added to the residue, which was then filtered. The solvent was evaporated under vacuum and the product was dried. The precipitate was recrystallized from ethanol to give compounds 6a–h in excellent yields of 83–86%.

Ethyl–2-((pyridin-4-yl)methylthio)-4-(4-fluorophenyl)-1,2-dihydro-6-methylpyrimidine-5-carboxylate (6a), 84% yield, m.p. 201–203°C. Anal. calcd. for $C_{20}H_{20}FN_3O_2S$ (385.12): C, 62.32; H, 5.23; N, 10.90. Found: C, 62.29; H, 5.19; N, 10.85. IR (KBr, cm^{-1}): 3345 (NH), 1720 (CO ester), 1270 (C-S), 1100 (C-F). ^{1}H-NMR (DMSO-d_6, δ ppm): 1.98 (3H, s, CH_3), 2.15 (3H, t, $COOCH_2CH_3$), 3.85 (2H, q, $COOCH_2CH_3$), 3.90 (2H, s, CH_2S), 5.60 (1H, s, CH), 6.80–7.10 (4H, m, CH-aromatic), 7.20–7.35 (4H, m, CH-aromatic pyridine), 9.75 (1H, s, NH exchangeable with D_2O). MS: *m/z*=385 [M^+].

Ethyl–2-((pyridin-4-yl)methylthio)-4-(4-chlorophenyl)-1,2-dihydro-6-methylpyrimidine-5-carboxylate (6b), 83% yield, m.p. 223–225°C. Anal. calcd. for $C_{20}H_{20}ClN_3O_2S$ (401.91): C, 59.77; H, 8.82; N, 10.46; S, 7.98, 5.02, Cl. Found: C, 59.73; H, 7.78; N, 10.41; S, 7.94, 4.49, Cl. IR (KBr, cm^{-1}): 3355 (NH), 1725 (CO ester), 1267 (C–S), 1090 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.00 (3H, s, CH_3), 2.20 (3H, t, $COOCH_2CH_3$), 3.80 (2H, q, $COOCH_2CH_3$), 4.10 (2H, s, CH_2S), 5.75 (1H, s, CH), 6.90–7.20 (4H, m, CH-aromatic), 7.30–7.45 (4H, m, CH-aromatic pyridine), 9.65 (1H, s, NH exchangeable with D_2O). MS: *m/z*=401 [M^+] and 403 [M^+ +2].

Ethyl-2-((pyridin-4-yl)methylthio)-1,2-dihydro-6-methyl-4-(4-(thiophen-2yl)phenyl)pyrimidine-5-carboxylate (6c), 85% yield, m.p. 229–231°C. Anal. calcd. for $C_{24}H_{23}N_3O_2S_2$ (449.123): C, 64.12; H, 5.16; N, 9.35; S, 14.26. Found: C, 64.10; H, 5.14; N, 9.32. IR (KBr, cm^{-1}): 3340 (NH), 1700 (CO ester), 1269–1275 (C-S). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.15 (3H, s, CH_3), 2.30 (3H, t, $COOCH_2CH_3$), 3.90 (2H, q, $COOCH_2CH_3$), 4.20 (2H, s, CH_2S), 5.85 (1H, s, CH), 6.20–6.40 (3H, m, CH-thiophene), 7.20–7.35 (4H, m, CH-aromatic pyridine), 9.55 (1H, s, NH exchangeable with D_2O).

Ethyl–2-((pyridin-4-yl)methylthio)-4-(4-(furan-2-yl)phenyl)-1,2-dihydro-6-methylpyrimidine-5-carboxylate (6d), 84% yield, m.p. 255–257°C. Anal. calcd. for $C_{24}H_{23}N_3O_3S$ (433.146): C, 66.49; H, 5.35; N, 9.69; S, 7.40. Found: C, 66.46; H, 5.30; N, 9.63; S, 7.37. IR (KBr, cm^{-1}): 3350 (NH), 1715 (CO ester), 1270 (C–S), 1110 (C–F). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.20 (3H, s, CH_3), 2.35 (3H, t, $COOCH_2CH_3$), 3.85 (2H, q, $COOCH_2CH_3$), 3.98 (2H, s, CH_2S), 5.78 (1H, s, CH), 6.28–6.46 (3H, m, CH-furan), 7.30–7.45 (4H, m, CH-aromatic pyridine), 9.85 (1H, s, NH exchangeable with D_2O).

Ethyl-2-((pyridin-4-yl)methoxy)-4-(4-fluorophenyl)-1,2-dihydro-6-methylpyrimidine-5-carboxylate (6e), 83% yield, m.p. 245–247°C. Anal. calcd. for $C_{20}H_{20}FN_3O_3$ (369.149): C, 65.03; H, 5.46; F, 5.14; N, 11.38. Found: C, 65.00; H, 5.42; N, 11.35. IR (KBr, cm^{-1}): 3340 (NH), 1719 (CO ester), 1640 (C=N), 1260 (C-S), 1120 (C-F). ^{1}H-NMR (DMSO-d_6, δ ppm): 1.90 (3H, s, CH_3), 2.25 (3H, t, $COOCH_2CH_3$), 3.98 (2H, q, $COOCH_2CH_3$), 4.59 (2H, s, CH_2O), 5.70 (1H, s, CH), 6.80–7.00 (4H, m, CH-aromatic), 7.15–7.35 (4H, m, CH-aromatic pyridine), 8.95 (1H, s, NH exchangeable with D_2O). MS: *m/z*=369 [M^+].

Ethyl–2-((pyridin-4-yl)methoxy)-4–(4-chlorophenyl)-1,2-dihydro-6-methylpyrimidine-5-carboxylate (6f), 83% yield, m.p. 260-262°C. Anal. calcd. for $C_{20}H_{20}ClN_3O_3$ (385.119): C, 62.26; H, 5.22; Cl, 9.19; N, 10.89. Found: C, 62.21; H, 5.18; Cl, 9.15; N, 10.86. IR (KBr, cm^{-1}): 3345 (NH), 1725 (CO ester), 1626 (C=N), 1265 (C–S), 1080 (C–Cl). ^{1}H–NMR (DMSO–d_6, δ ppm): 1.95 (3H, t, CH_3), 2.30 (3H, t, $COOCH_2CH_3$), 3.95 (2H, q, $COOCH_2CH_3$), 4.55 (2H, s, CH_2O), 5.85 (1H, s, CH), 6.80–7.00 (4H, m, CH-aromatic), 7.15–7.35 (4H, m, CH-aromatic pyridine), 8.89 (1H, s, NH exchangeable with D_2O). MS: *m/z*=385 [M^+] and 387 [M^+ +2].

Ethyl–2–((pyridin–4–yl)methoxy)–1,2–dihydro–6–methyl–4–(4–(thiophen–2–yl)phenyl)pyrimidine–5–carboxylate (6g), 85% yield, m.p. 209–211°C. Anal. calcd. for $C_{24}H_{23}N_3O_3S$ (433.146): C, 66.49; H, 5.35; N, 9.69; S, 7.40. Found: C, 66.46; H, 5.30; N, 9.64; S, 7.36. IR (KBr, cm^{-1}): 3338 (NH), 1700 (CO ester), 1630 (C=N), 1257 (C–S). ^{1}H–NMR (DMSO–d_6, δ ppm): 1.80 (3H, s, CH_3), 2.25 (3H, t, $COOCH_2CH_3$), 3.95 (2H, q, $COOCH_2CH_3$), 4.50 (2H, s, CH_2O), 5.75 (1H, s, CH), 6.10–6.35 (3H, m, CH-thiophene), 7.20–7.40 (4H, m, CH-aromatic pyridine), 8.85 (1H, s, NH exchangeable with D_2O).

Ethyl-2-((pyridin-4-yl)methoxy)-4–(4-(furan-2-yl) phenyl)-1,2-dihydro-6-methylpyrimidine-5-carboxylate (6h), 86% yield, m.p. 236–238 °C. Anal. calcd. for $C_{24}H_{23}N_3O_4$ (417.169): C, 69.05; H, 5.55; N, 10.07. Found: C, 69.02; H, 5.50; N, 10.04. IR (KBr, cm^{-1}): 3348 (NH), 1718 (CO ester), 1640 (C=N), 1269 (C–S). ^{1}H–NMR (DMSO-d_6, δ ppm): 1.50 (3H, s, CH_3), 2.10 (3H, t, $COOCH_2CH_3$), 4.00(2H, q, $COOCH_2CH_3$), 4.70 (2H, s, CH_2O), 5.60 (1H, s, CH), 6.00–6.20 (3H, m, CH–furan), 7.15-7.35 (4H, m, CH-aromatic pyridine), 8.75 (1H, s, NH exchangeable with D_2O).

Results and discussion

The reaction routes for the synthesis of the title compounds are described in Schemes 1 and 2.

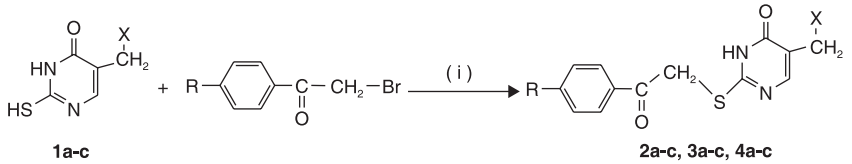
Compounds 2-thioxo-2,3-dihydropyrimidin-4(1H)-one derivatives 1a–c were synthesized by adopting the procedure reported in the study by Singh *et al.* [23] by the reaction of 2-thiouracil with mopholine or *N*-methylpiprazine or pipyridine under reflux. Compounds 1a–c were allowed to react with phenacyl bromide or 4-methyl phenacyl bromide or 4-nitrophenacyl bromide in the presence of sodium ethoxide under reflux to give the corresponding products 5-[(morpholin-4-ylmethyl)]-2-oxoethyl-sulfanyl pyrimidin-4(3H)-one derivatives (2a–c), 5-[(4-methylpiperazin-1-yl)]methyl sulfanyl-pyrimidin-4(3H)-one derivatives (3a–c), and 5–[(piperidin-1-yl)methyl]sulfanyl-pyrimidin-4(3H)-one derivatives (4a-c), respectively (Scheme 1). The spectral data of all the synthesized compounds 2a–c, 3a–c, and 4a–c were established on the basis of elemental analysis and spectral data (c.f. experimental data). The IR spectra of compounds 2a–c revealed the absorption bands at 3340–3350 cm^{-1} (NH), 1670–1685 cm^{-1} (C=O groups), and 1270–1278 cm^{-1} corresponding to C=S groups, respectively. The IR spectra of compounds 3a–c indicated the presence of NH absorption bands at 3340–3350 cm^{-1} in addition to C=O bands at 1670–1689 cm^{-1}. The IR spectra of compounds 4a–c showed absorption bands at 3340–3355 cm^{-1} (NH) and at 1675–1685 cm^{-1} (carbonyl groups).

Compounds 5a–h were previously prepared according to Biginelli reaction [24–27]. To improve the yield, the reaction was carried out in the presence of catalytic amount of silica sulfuric acid (SSA) and para toluene sulfonic acid (P-TSA) as heteroogeneous catalyst. SSA is an inorganic acidic catalyst that has recently attracted some interest in organic reactions [28,29]. The yield was improved to 88%.

Heterogeneous reagent systems have many advantages such as simplicity of use, mild reaction conditions, minimization of chemical waste, and good yields. In contrast, the use of heterogeneous solid catalysts in the organic synthesis and industrial manufacture of chemicals is interesting and of value because of their suitable acidity, insolubility to all organic solvents, thermal stability, and low cost; they also provide an eco-friendly [30–31].

However, the best result was obtained when the reaction was carried out in the presence of 5wt% of nano-copper Y Zeolite in ethanol, encouraged by the

Scheme 1



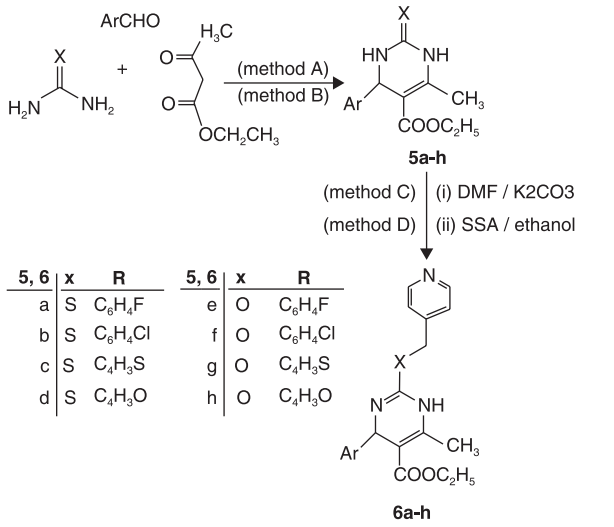
2	a	b	c
R	H	CH_3	NO_2
x	morpholine		

3	a	b	c
R	H	CH_3	NO_2
x	N-methylpiprazine		

4	a	b	c
R	H	CH_3	NO_2
x	piperidine		

General procedure for the synthesis 5-[(morpholin-4-ylmethyl)]-2-oxoethyl-sulfanyl pyrimidin-4(3H)-one derivatives (2a-c), 5-[(4-methylpiperazin-1-yl)]methyl sulfanyl-pyrimidin-4(3H)-one derivatives (3a-c) and 5-[(piperidin-1-yl)methyl]sulfanyl-pyrimidin-4(3H)-one derivatives (4a-c). Conditions and reagents: (i) phenacyl bromide, 4-methyl phenacyl bromide or 4-nitrophenacyl/ sodium ethoxide/reflux.

Scheme 2



5, 6	x	R
a	S	C_6H_4F
b	S	C_6H_4Cl
c	S	C_4H_3S
d	S	C_4H_3O

5, 6	x	R
e	O	C_6H_4F
f	O	C_6H_4Cl
g	O	C_4H_3S
h	O	C_4H_3O

General procedure for the synthesis 1,2 dihydropyrimidone derivatives (5a-h) and ethyl-2-((pyridin-4-yl)methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives (6a-h). Method C: urea or thiourea/ 4-flourobenzaldehyde, 4-chlorobenzaldehyde, 2-thiophene aldehyde or 2-furfuraldehyde/ketoester /silica sulfuric acid /silica gel/P-TSA/ ethanol /100 0C. Method D: urea or thiourea/4-flourobenzaldehyde, 4-chlorobenzaldehyde, 2-thiophene aldehyde or 2-furfuraldehyde/ ketoester/ethanol/nano-CuY Zeolite catalyst.

above result and the development and generality of this simple method as a fairly good catalyst for this reaction. The method is associated with several advantages such as simplicity of use, milder conditions, short reaction times, excellent yields, and reusability of the catalyst. Transition CuY-Zeolite is an efficient nanocatalyst that is clean and eco-friendly [32–36].

When compounds 5a–h were reacted with 4-picolyl chloride under basic conditions and in the presence of potassium carbonate in DMF or SSA in ethanol, the corresponding products ethyl-2-((pyridin-4-yl) methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives 6a–h were obtained (Scheme 2). The structures of compounds 6a–d were established on the basis of elemental analysis and spectral data. The IR spectrum of 6a revealed absorption bands at 3345 cm^{-1} attributed to the NH group, at 1720 cm^{-1} for the CO ester group, and at 1100 cm^{-1} for the C–F group. In addition, the mass spectrum showed ion peak [M^+] at m/z=385, which was in agreement with the calculated molecular weight. In a similar manner, the IR spectrum of compound 6b showed absorption bands at 3355 cm^{-1} for NH, at 1725 cm^{-1} for the CO ester group, and at 1090 cm^{-1} for C–Cl. The mass spectrum revealed ion peak [M^+] at m/z=401 and 403/3 : 1 abundance, which was in agreement with the calculated molecular weight of compound 6b. The IR spectrum of compound 6c showed absorption band due to the NH group at 3340 cm^{-1} and the presence of CO ester group at 1700 cm^{-1}, and its ^{1}H–NMR spectrum displayed signals at 2.15 (CH_3), 4.20 (CH_2S), 7.20–7.35 (CH-aromatic proton), and 9.55 (NH) ppm, respectively. The IR spectrum of compound 6d revealed absorption bands at 3350 cm^{-1} for NH and at 1715 cm^{-1} for the CO ester group. The ^{1}H–NMR spectrum of compound 6d showed signals due to 2.20 (CH_3), 3.98 (CH_2S), 7.30–7.45 (CH-aromatic proton), and 9.85 (NH) ppm, which supported the suggested structures (c.f. experimental data).

The structure of compounds 6e–h was assigned on the basis of their elemental analyses and spectral data. The IR spectra of 6e–h revealed absorption bands at 3338–3348 cm^{-1} (NH groups) and 1718–1725 cm^{-1} (CO ester groups), in addition to at 1260–1269 cm^{-1} (C–S groups), 1120 cm^{-1} (C–F), and 1080 cm^{-1} (C–Cl). In addition, the mass spectrum of compound 6e showed ion peak [M^+] at m/z=369 and the mass spectrum of compound 6f revealed ion peak [M^+] at m/z=385 and 387/3 : 1 abundance, which supported the structure of compound 6f (c.f. experimental data).

Conclusion

The synthesis of new heterocyclic pyrimidines was performed in good yields. These compounds could be considered as interesting analogs of pyrimidines used in biological applications. A series of sulfanylpyrimidin-4(3H)-one derivatives have been prepared in good yield. Sulfanylpyrimidin-4(3H)-one derivatives were incorporated into a ring of morpholine, methylpiprazine, and piperidin through a sulfanyl bridge at position 5 to form compounds (2a–c), (3a-c), and (4a–c). Ethyl-2-((pyridin-4-yl)methoxy-1,2-dihydro-6-methyl-pyrimidine derivatives 6a–h were prepared using conventional and heterogeneous conditions such as SSA as an efficient catalyst for the preparation of pyrimidine derivatives and nano-copper Y Zeolite to improve the yield to optimize the reaction conditions. We believe that the present method would be an important addition to existing methodologies.

Acknowledgements

The authors are grateful to the National Research Center for supporting this work.

Conflicts of interest

None declared.

References

1 Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, Hedberg A, O'Reilly BC. Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. J Med Chem 1991; 34:806–811.

2 Kappe CO. Biologically active dihydropyrimidones of the Biginelli-type – a literature survey. Eur J Med Chem 2000; 35:1043–1052.

3 Patel RB, Desai PS, Desai KR, Chikhalia KH. Synthesis and biological activity of some 2,4,6-trisubstituted-1,3,5-s-triazines. J Indian Chem Soc 2003; 80:138–140.

4 Kappe CO. 4-Aryldihydropyrimidines via the Biginelli condensation: Aza-analogs of nifedipine-type calcium channel modulators. Molecules 1998; 3:1–9.

5 Cordeu L, Cubedo E, Bandrés E, Rebollo A, Sáenz X, Chozas H, *et al.* Biological profile of new apoptotic agents based on 2,4-pyrido[2,3-d] pyrimidine derivatives. Bioorg Med Chem 2007; 15:1659–1669.

6 Wang Y-P, Chen F-E, De Clercq E, Balzarini J, Pannecouque C. Synthesis and *in vitro* anti-HIV evaluation of a new series of 6-arylmethyl-substituted S-DABOs as potential non-nucleoside HIV-1 reverse transcriptase inhibitors. Eur J Med Chem 2009; 44:1016–1023.

7 El-Gazzar A-R, El-Enany MM, Mahmoud MN. Synthesis, analgesic, anti-inflammatory, and antimicrobial activity of some novel pyrimido[4,5-b] quinolin-4-ones. Bioorg Med Chem 2008; 16:3261–3273.

8 Bernier JL, Henichart JP, Warin V, Baert F. Synthesis and structure–activity relationship of a pyrimido[4,5-d]pyrimidine derivative with antidepressant activity. J Pharm Sci 1980; 69:1343–1345.

9 Powers DL, Sowell Sr JW, Freeman JJ, Kosh JW. Anticonvulsant properties of selected pyrrolo[2,3-d]pyrimidine-2,4-diones and intermediates. J Pharm Sci 1980; 69:473–475.

10 El-Agrody AM, Ali FM, Eid FA, El-Nassag MAA, El-Sherbeny G, Bedair AH. Synthesis and antimicrobial activity of thioxopyrimidines and related derivatives. Phosphorus Sulfur Silicon Relat Elem 2006; 181:839–864.

11 Huang T, Tu H Aibibu Z, Hou C, Zhang A. Synthesis and herbicidal activity of new substituted 2- and 4-pyrimidinyloxy-phenoxypropionate derivatives. ARKIVOC 2011; (ii):1–17.

12 Singour PK, Khare A, Dewangan H, Pawar RS. Synthesis and biological evaluation of novel pyrimidine derivatives as anti-inflammatory agents. J Pharm Res 2012; 5:4853–4858.

13 Ahmada M, Sastry V, Prasada Y, Khanb M, Banob N, Anwarc S. Conventional and microwave assisted synthesis of 2-amino-4,6-diarylpyrimidine derivatives and their cytotoxic, anti-oxidant activities. Eur J Chem 2012; 3:94–98.

14 Prafulla BC, Swapnil DJ, Rakesh PD, Manish SB, Suhel SS, Kundan BI, Neela M. Development of pyrimidine derivatives as selective Cox-2 inhibitors. Am Eurasian J Sci Res 2012; 7:69–76.

15 Ballell L, Field RA, Chung GAC, Young RJ. New thiopyrazolo[3,4-d] pyrimidine derivatives as anti-mycobacterial agents. Bioorg Med Chem Lett 2007; 17:1736–1740.

16 Ukrainets IV, Tugaibei IA, Bereznykova NL, Karvechenko VN, Turov AV. Analgesic, anticonvulsant and anti-inflammatory activities of some synthesized benzodiazipine, triazolopyrimidine and bis-imide derivatives. Chem Heterocycl Compd 2008; 44:565–575.

17 Wang SQ, Fang L, Liu XJ, Zhao K. Design, synthesis, and hypnotic activity of pyrazolo[1,5-a]pyrimidine derivatives. Chin Chem Lett 2004; 15:885–888.

18 Yang W, Ruan Z, Wang Y, Van Kirk K, Ma Z, Arey BJ, *et al.* Discovery and structure–activity relationships of trisubstituted pyrimidines/pyridines as novel calcium-sensing receptor antagonists. J Med Chem 2009; 52: 1204–1208.

19 Gillespie RJ, Bamford SJ, Botting R, Comer M, Denny S, Gaur S, *et al.* Antagonists of the human A2A adenosine receptor. 4. Design, synthesis, and preclinical evaluation of 7-aryltriazolo[4,5-d]pyrimidines. J Med Chem 2009; 52:33–47.

20 He Y-P, Long J, Zhang S-S, Li C, Lai CC, Zhang C-S, *et al.* Synthesis and biological evaluation of novel dihydro-aryl/alkylsulfanyl-cyclohexylmethyl-oxopyrimidines (S-DACOs) as high active anti-HIV agents. Bioorg Med Chem Lett 2011; 21:694–697.

21 Novikov MS, Ozerov AA, Sim OG, Buckheit RW. Synthesis and anti-HIV-1 activity of 2-[2-(3,5-dimethylphenoxy)-ethylthio] pyrimidin-4(3H)-ones. Chem Heterocycl Compd 2004; 40:37–42.

22 Barot VM, Mitesh CP. Synthesis and biological evaluation of pyrimidine-2-thiones. Asian J Biochem Pharma Res 2013; 3:111–115.

23 Singh BK, Mishra M, Saxena N, Yadav GP, Maulik PR, Sahoo MK, *et al.* Synthesis of 2-sulfanyl-6-methyl-1,4-dihydropyrimidines as a new class of antifilarial agents. Eur J Med Chem 2008; 43:2717–2723.

24 Elżbieta W, Tomasz P. Thio analogs of pyrimidine bases: syntheses and EIMS study of new ortho-(meta- and para-)bromobenzyl s-mono and S-N-1-disubstituted 5-morpholinomethyl(5-piperidinomethyl)-2-thiouracils, J Heterocyclic Chem 2007; 55–61.

25 Akbas E, Levent A, Gümüş S, Sümer MR, Akyazi I. Synthesis of some novel pyrimidine derivatives and investigation of their electrochemical behavior. Bull Korean Chem Soc 2010; 31:3632–3638.

26 Flasone FS, Kappe CO. The Biginelli dihydropyrimidone synthesis using polyphosphate ester as a mild and efficient cyclocondensation/dehydration reagent. ARKIVOC 2001; (ii):122–134.

27 Syamala M. Recent progress in three-component reactions. An update. Org Prep Proced Int 2009; 41:1–68.

28 Vanden Eynde JJ, Audiart N, Canonne V, Michel S, Van Haverbeke Y, Oliver Kappe C. Synthesis and aromatization of dihydropyrimidines structurally related to calcium channel modulators of the nifedipine-type. Heterocycles 1997; 45:1967–1978.

29 Dabiri M, Salehi P, Baghbanzadeh M, Zolfigol MA, Agheb M, Heydari S. Silica sulfuric acid: an efficient reusable heterogeneous catalyst for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones in water and under solvent-free conditions. Catal Commun 2008; 9:785–788.

30 Salehi P, Zolfigol MA, Shirini F, Baghbanzadeh M. Silica sulfuric acid and silica chloride as efficient reagents for organic reactions. Curr Org Chem 2006; 10:2171–2189.

31 Hamid RS, Majid G, Mostafa F. Silica sulfuric acid as an efficient catalyst for the preparation of 2H-indazolo[2,1b]phthalazine-triones. Appl Catal A-Gen 2008; 345:128–133.

32 Bournay L, Casanave D, Delfort B, Hillion G, Chodorge JA. New heterogeneous process for biodiesel production: a way to improve the quality and the value of the crude glycerin produced by biodiesel plants. Catal Today 2005; 106:190–192.

33 Do PTM, McAtee JR, Watson DA, Lobo RF. Elucidation of Diels–Alder reaction network of 2,5-dimethylfuran and ethylene on HY zeolite catalyst. ACS Catal 2013; 3:41–46.

34 Takamitsu Y, Yoshida S, Kobayashi W, Ogawa H, Sano T. Combustion of volatile organic compounds over composite catalyst of Pt/γ-Al 2O 3 and beta zeolite. J Environ Sci Health A Tox Hazard Subst Environ Eng 2013; 48:667–674.

35 Dapsens PY, Mondelli C, Pérez-Ramírez J. Highly selective lewis acid sites in desilicated MFI zeolites for dihydroxyacetone isomerization to lactic acid. ChemSusChem 2013; 6:831–839.

36 Mehdi K, Nooshin K, Mojgan Z Facile synthesis of 2-arylbenzimidazoles by nano-CuY zeolite as an efficient and eco-friendly nanocatalyst. Lett Org Chem 2013; 10:573–577.