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NEW THEOPYRIMIDINE DERIVATIVES OF EXPECTED ANTIINFLAMMATORY ACTIVITY

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ABSTRACT

The pyrimidine derivatives 1-(4-aryl-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-yl)-ethanone (1a-c) were obtained from the reaction of thiourea with acetylacetone and aromatic aldehydes and utilized for synthesis of a number of thiopyrimidine derivatives (2a-i to 6a-f). Some of the newly synthesized compounds were preliminary tested for their antibacterial activity, and several compounds were tested for anti-inflammatory activity. Compounds, 4-aryl-6-methyl-5-(1-(arylimino) ethyl)-1, 2,3,4-tetrahydropyrimidine-2(1H)-thiones 2a, 2c, 2f, 2i, 1-(4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(arylamino)-propan-1-ones 3c, 3f and 6-methyl-4-styryl-5-(5-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-1,2,3,4-tetrahydro pyrimidine-2-(1H)-thione (5b) were found to be effective as anti-inflammatory agents in vivo.

Keywords: Thiopyrimidine, Pyrimidine, Anti- inflammatory activity.

INTRODUCTION

Pyrimidine moiety is an important class of nitrogen containing heterocycles [1] and is widely used as a key building block for pharmaceutical agents. Its derivatives exhibit antibacterial, antifungal [2], analgesic [3], calcium antagonist [4], anti-inflammatory [5] and anti-tumor activity [6]. In addition, several marine natural products with interesting biological activities containing pyrimidine core have recently been isolated [7]. Most notably among these are the batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy. In 1893, Biginelli reported one-step reaction for synthesis of 3,4-dihydropyrimidine-2-(*1H*)-one by three-component raction of ethyl acetoacetate, urea and benzaldehyde [8]. These Biginelli compounds possess several biological activities like antibacterial, antiviral, antitumor and anti-inflammatory [9-11].In continued quest of new anti-inflammatory agents we herein report the synthesis of certain thiopyrimidine derivatives and their anti-inflammatory activity.

MATERIALS AND METHODS

Chemistry

Pyrimidine thione derivatives 1a-c were prepared by condensation of thiourea with the appropriate aromatic aldehyde and acetyl acetone based on the previously reported similar methods [12-15].Their IR

spectra showed characteristic bands of the C=O groups at 1675, 1680, and 1686 cm^{-1} respectively and broad bands at 2279-2366 cm^{-1} characteristic for NH of pyrimidine. While their ^{1}H-NMR showed singlet at 9-10 ppm corresponding to the D_2O exchangeable protons of 1,3 NH of the pyrimidine ring.Compounds 1a-c reacted with some primary amines and hydrazine hydrate to yield Schiff's bases 2a-f and hydrazones 2g-i, respectively. The IR spectra of 2a-c, 2g-i revealed the absence of the absorption bands corresponding to the C=O group, while, that of 2g-i displayed absorption bands around 3300 cm^{-1} corresponding to NH_2 group. On the other hand, reaction of 1a-c with paraformaldehyde and certain primary aromatic amines afforded the respective Mannich bases 3a-f. Their IR spectra showed the presence of absorption bands at 1681-1700 cm^{-1} characteristic for the C=O groups. Their ^{1}H-NMR spectra showed triplets of the four protons CH_2-CH_2 at the range 3.1-3.7 ppm.

Chalcone derivatives 4a-f were formed by the reaction of 1a-c with some aromatic aldehydes. Their IR spectra showed absorption bands at the carbonyl region 1681-1749 cm^{-1} while, their ^{1}H-NMR spectra showed doublet-doublet of CH=CH of the chalcones at the range 4.7-5.5 ppm. Chalcones 4a-f further reacted with phenylhydrazine and with thiourea to give the corresponding pyrazoles 5a-f and pyrimidine thiones 6a-f. Their IR spectra revealed the absence of the carbonyl groups and the appearance of the bands corresponding to C=N around 1600 cm^{-1} and C=S around 1200 cm^{-1} in 5a-f and 6a-f respectively, While their ^{1}H-NMR showed the disappearance of the doublet-doublet corresponding to CH=CH of the chalcones (Scheme 1).

Reagents, Instrumentation and Measurements

Experimental

All melting points are uncorrected and were measured using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (USA), Faculty of Science, Cairo University, Cairo, Egypt. ^{1}H-NMR spectra were determined using (DMSO-d_6) solvent on a Varian Mercury (300 MHz) spectrometer (Varian, UK) and chemical shifts (δ) were expressed as ppm against TMS as internal reference, Faculty of Science, Cairo University, Cairo, Egypt. Mass spectra were recorded on a 70 eV EI Ms-QP 1000 EX (Shimadzu), Faculty of Science, Cairo University, Cairo, Egypt. Microanalyses were operated using Vario, Elementar apparatus (Shimadzu), Faculty of Science, Cairo University, Cairo, Egypt.

The progress of all the reactions was monitored by thin layer chromatography on silica gel 60 for TLC (Merck) using chloroform-ethanol (3:1) as mobile phase and spots were visualized by iodine vapours or by irradiation with UV light (254 nm). Column chromatography was performed on (Merck) silica gel 60 (particle size 0.06-0.20 mm).

The results of the micro analysis of all the synthesized compounds were within accepted range (± 0.40 %) of the calculated values.

General procedure for preparation of compound 1

A mixture of thiourea (0.76g, 0.01 mol), appropriate aromatic aldehyde (0.01 mol) and acetylacetone(1.0 mL, 0.01 mol) in absolute ethanol (20 mL) containing 37 % HCl (8 drops) was refluxed for 8 hours, the reaction solution allowed to cool. The resulting precipitate was filtered off and washed with 50 % ethanol, dried, recrystallized from ethanol to afford 1a-c.

1-(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)ethanone (1a)

Yield: 86 %. m.p. 197-199° C. IR (KBr) υ (cm^{-1}): 3366 (NH), 1680 (C=O) 1243 (C=S). MS (EI) m/z: 246 (M^+, 77%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.60 (s, 3H, CH_3, pyrimidine), 2.70 (s, 3H, $COCH_3$), 5.26 (s, 1H pyrimidine), 7.23-7.33 (m, 5H, Ar-H), 9.60, 9.70 (2H, 2NH, D_2O exchangeable).

Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37; S, 13.02 %. Found: C, 63.15; H, 5.54; N, 11.24; S, 12.72%.

1-(6-Methyl-4-(4-methoxy-phenyl)-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-yl)ethanone (1b)

Yield: 88 %. m.p. 179-181 °C. IR (KBr) υ (cm-1): 3336 (NH), 1675 (C=O), 1226 (C=S). MS (EI) m/z: 276 (M+, 100 %). 1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.25 (s, 3H, CH3, pyrimidine), 2.60 (s, 3H, $COCH_3$), 3.83 (s, 3H, OMe), 5.12 (s, 1H pyrimidine), 7.20 (dd, *J= 8.1*, 2.3 Hz, 4H, Ph-OCH_3), 9.69, 9.73 (2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; S, 11.60 %. Found: C, 60.59; H, 5.72; N, 9.98; S, 11.30 %.

1-(6-Methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)ethanone (1c)

Yield: 90 %. m.p. 183-185 °C. IR (KBr) υ (cm^{-1}): 3279.36 (NH), 1686.44 (C=O), 1620 (C=S). MS (EI) m/z: 272 (M^+, 21.4 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.26 (s, 3H, CH_3, pyrimidine), 2.30 (s, 3H, CH_3), 5.00 (d, *J*= 8.1 Hz, 1H, pyrimidine), 6.2 (t, *J*= 7.1 Hz, 1H, CH, CH=CH), 6.4 (d, *J*= 8.1 Hz, 1H, CH=CH), 7.2-7.8 (m, 5H, Ar-H), 9.6-10.4 (s, 2H , 2NH, D_2O exchangeable). Anal. Calcd. for $C_{15}H_{16}N_2OS$ (272.37): C, 66.15; H, 5.92; N, 10.28; O, 5.87; S, 11.77 %. Found: C, 66.00; H, 5.73; N, 10.14; O, 5.50; S, 11.49 %.

General procedure for preparation of compound 2

To a solution of the appropriate pyrimidine derivative 1a-c (0.01 mol) in dry methanol (50 mL) containing 1 % conc. H_2SO_4, the appropriate primary amine and hydrazine hydrate were added. The reaction mixture was heated under reflux for three hours; the resulting product was cooled, poured onto ice-water (200 mL) and neutralized with 25 % ammonia solution (0.5 mL). The precipitate formed was filtered and recrystallized from methanol to give compounds 2a-i.

6-Methyl-4-styryl-5(1-(phenylimino)ethyl)-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (2a)

Yield: 85 %. m.p. 182-184 °C. IR (KBr) υ (cm^{-1}): 3400 (NH), 1586 (C=N), 1620 (C=S). MS (EI) m/z: 347 (M^+, 33 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.07 (s, 3H, CH_3), 2.26 (s, 3H, CH_3, pyrimidine), 4.99 (s, 1H, pyrimidine), 6.19 (t, *J*= 8.1 Hz, 1H, CH, CH=CH), 6.51 (d, *J*= 8.1 Hz, 1H, CH, CH=CH), 6.9-7.54 (m, 10H, Ar-H), 9.68, 9.73 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{21}H_{21}N_3S$ (347.49): C, 72.59; H, 6.09; N, 12.09; S, 9.23 %. Found: C, 72.27; H, 5.73; N, 11.73; S, 9.00 %.

6-Methyl-4-phenyl-5(1-(phenylimino)ethyl)-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (2b)

Yield: 87 %. m.p. 180-182 °C. IR (KBr) υ (cm^{-1}): 3389.4 (NH), 1590 (C=N), 1623 (C=S). MS (EI) m/z: 321 (M^+, 73 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.07 (s, 3H, CH_3), 2.26 (s, 3H, CH_3, pyrimidine), 5.16 (s, 1H, pyrimidine), 6.98-7.45 (m, 10H, Ar-H), 9.68, 9.73 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{19}H_{19}N_3S$ (321.45): C, 71.00; H, 5.96; N, 13.07; S, 9.97 %. Found: C, 70.67; H, 5.59; N, 12.99; S, 9.65 %.

6-Methyl-4-(4-methoxyphenyl)-5(1-(phenylimino)ethyl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (2c)

Yield: 84 %. m.p. 140-142 °C. IR (KBr) υ (cm^{-1}): 3389.3 (NH), 1594.6 (C=N), 1605 (C=S). MS (EI) m/z: 351 (M^+, 77 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3, pyrimidine), 3.74 (s, 3H, CH_3, OMe), 5.19 (s, 1H pyrimidine), 6.81-7.36 (m, 9H, Ar-H), 9.3, 9.5 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{20}H_{21}N_3OS$ (351.74): C, 68.35; H, 6.02; N, 11.96; S, 9.12 %. Found: C, 68.00; H, 5.79; N, 11.82; S, 8.86 %.

6-Methyl-4-styryl-5(1-(4-acetophenylimino)ethyl)-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (2d)

Yield: 71 %. m.p. 283-285 °C. IR (KBr) υ (cm^{-1}): 3299.7 (NH), 1600 (C=N), 1693 (C=O). MS (EI) m/z: 389 (M^+ , 43 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.24 (s, 3H, CH_3), 2.26 (s, 3H, CH_3, pyrimidine), 2.50 (s, 3H, CH_3, C=OMe), 4.99 (d, *J*=7.1 Hz, 1H pyrimidine), 6.19 (t, *J*=7.3 Hz, 1H, CH, CH=CH), 6.56 (d, *J*=7.3 Hz, 1H, CH=CH), 7.24-7.35 (m, 9H, Ar-H), 9.74, 10.55 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for: $C_{23}H_{23}N_3OS$ (389.52): C, 70.92; H, 5.95; N, 10.79; S, 8.32 %. Found: C, 70.63; H, 5.74 N, 10.52; S, 8.00 %.

6-Methyl-4-phenyl-5(1-(4-acetophenylimino)ethyl)-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (2e)

Yield: 70 %. m.p.165-167°C. IR (KBr) ν (Cm^{-1}): 3350 (NH), 1630 (C=N), 1685 (C=O). MS (EI) m/z: 363 (M^+ , 74 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.20 (s, 3H, CH_3), 2.27 (s, 3H, CH_3, pyrimidine), 2.45 (s, 3H, CH_3, C=OMe), 5.12 (s, 1H pyrimidine), 7.2-7.36 (m, 9H, Ar-H), 9.5, 9.64 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for: $C_{21}H_{21}N_3OS$ (363.49): C, 69.39; H, 5.82; N, 11.56; S, 8.82 %. Found: C, 69.27; H, 5.58; N, 11.27; S, 8.52 %.

6-Methyl-4-(4-methoxyphenyl)-5(1-(4-acetophenylimino)ethyl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (2f)

Yield: 90 %. m.p. 180-182°C. IR (KBr) ν (Cm^{-1}): 3357 (NH), 1635 (C=N), 1690 (C=O). MS (EI) m/z: 393 (M^+, 32 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.01 (s, 3H, CH_3), 2.33 (s, 3H, CH_3, pyrimidine), 2.43 (s, 3H, CH_3, C=OMe), 4.83 (s, 3H, CH_3, OMe), 5.00 (s, 1H pyrimidine), 6.89, 8.4 (m, 8H, Ar-H), 9.3, 9.7 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for: $C_{22}H_{23}N_3O_2S$ (393.51): C, 67.15; H, 5.89; N, 10.68; S, 8.15 %. Found: C, 66.87; H, 5.67; N, 10.43; S, 7.78 %.

6-Methyl-4-styryl-5-(1-hydrazono-ethyl)-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (2g)

Yield: 88 %. m.p. 225-227°C. IR (KBr) ν (Cm^{-1}): 3365(NH), 1640(C=N), 3334-3340 (NH_2). MS (EI) m/z: 286 (M^+ , 8 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.03 (s, 3H, CH_3), 2.3 (s, 3H, CH_3, pyrimidine), 5.1 (d, *J*=7.1 Hz, 1H pyrimidine), 5.98 (s, 2H, NH_2, D_2O exchangeable), 6.2 (t, *J*=7.5 Hz, 1H, CH, CH=CH), 6.5 (d, *J*=7.5 Hz, H, CH, CH=CH), 7.2-7.3 (m, 5H, Ar-H), 9.6, 10.0 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{15}H_{18}N_4S$ (286.40): C, 62.91; H, 6.33; N, 19.56; S, 11.20 %. Found: C, 62.64; H, 5.99; N, 19.29; S, 10.89 %.

6-Methyl-4-phenyl-5-(1-hydrazono-ethyl)-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (2h)

Yield: 78 %. m.p. 265-267 °C. IR (KBr) ν (Cm^{-1}): 3367 (NH), 1652(C=N), 3329-3334(NH_2). MS (EI) m/z: 260 (M^+ , 54 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.14 (s, 3H, CH_3), 2.25 (s, 3H, CH_3, pyrimidine), 4.98 (s, 1H, pyrimidine), 5.95 (s, 2H, NH_2, D_2O exchangeable), 7.0-7.5 (m, 5H, Ar-H), 9.6, 9.7 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{13}H_{16}N_4S$ (260.36): C, 59.97; H, 6.19; N, 21.52; S, 12.32 %. Found: C, 59.65; H, 6.40; N, 21.79; S, 12.64 %.

6-Methyl-4-(4-methoxyphenyl)-5-(1-hydrazono-ethyl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (2i)

Yield: 67 %. m.p. 220-222 °C. IR (KBr) ν (Cm^{-1}): 3348 (NH), 1634 (C=N), 1260 (C=S), 3320-3324 (NH_2). MS (EI) m/z: 290 (M^+ , 100 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.07 (s, 3H, CH_3), 2.27 (s, 3H, CH_3, pyrimidine), 3.82 (s, 3H, CH_3, OMe), 5.00 (s, 2H, NH_2, D_2O exchangeable), 5.14 (s, 1H Pyrimidine), 7.2 (dd, *J*=8.2 Hz, 4H, Ph-OCH_3), 9.5, 9.7 (s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{14}H_{18}N_4OS$ (290.39): C, 57.91; H, 6.25; N, 19.29; S, 11.04 %. Found: C, 57.60; H, 6.50; N, 18.93; S, 11.31 %.

General procedure for preparation of compound 3

To a hot solution of paraformaldehyde (0.9 g, 0.01 mol) and the appropriate amine (0.01 mol) in absolute ethanol (25 mL), the appropriate pyrimidine derivative 1a-c (0.01 mol) in ethanol (10 mL) was added.

The reaction mixture was heated under reflux for three hours. Then it was cooled, and the precipitate formed was filtered off, dried, and recrystallized from methanol to afford compounds 3a-f.

1-(6-Methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(phenylamino)-propan-1-one (3a)

Yield: 73 %. m.p. 130-132 C. IR (KBr) ν (Cm^{-1}): 3335 (NH), 1682 (C=O), 1198 (C=S). MS (EI) m/z: 377 (M^+, 53 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.35 (s, 3H, CH_3, pyrimidine), 3.17 (t, *J*=7.1 Hz, 2H, CH_2), 3.28 (t, *J*=7.1 Hz, 2H, CH_2), 4.98 (d, *J*=7.3 Hz, 1H Pyrimidine), 5.8 (s, 1H, NH, D_2O exchangeable) 6.1 (t, *J*=7.1 Hz, 1H, CH, CH=CH), 6.5 (d, *J*=7.1 Hz, 1H, CH, CH=CH), 6.5-7.4 (m, 10H, Ar-H), 9.6, 9.5 (s, 2H, NH, Pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{22}H_{23}N_3OS$ (377.51): C, 70; H, 6.14; N, 11.13; S, 8.49 %. Found: C, 70.32; H, 6.00; N, 11.42; S, 8.29 %.

1-(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(phenylamino)-propan-1-one (3b)

Yield: 80 %. m.p. 240-242 °C. IR (KBr) ν (Cm^{-1}): 3400(NH), 1693(C=O) 1210 (C=S). MS (EI) m/z: 351(M^+, 45 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.26 (s, 3H, CH_3, pyrimidine), 3.20 (t, *J*=7.3 Hz, 2H, CH_2), 3.32 (t, *J*=7.3 Hz, 2H, CH_2), 5.16 (s, 1H Pyrimidine), 5.68 (s, 1H, NH, D_2O exchangeable), 6.8-7.5 (m, 10H, Ar-H), 9.70, 9.73 (s, 2H, 2NH, Pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{20}H_{21}N_3OS$ (351.47): C, 68.35; H, 6.02; N, 11.96; S, 9.12 %. Found: C, 68.62; H, 6.34; N, 11.67; S, 9.43 %.

1-(6-Methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(phenylamino)-propan-1-one (3c)

Yield: 69 %. m.p. 322-324°C. IR (KBr) ν (Cm^{-1}): 3420(NH), 1700(C=O) 1222 (C=S). MS (EI) m/z: 381 (M^+, 59 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.25 (s, 3H, CH_3, pyrimidine), 3.10 (t, *J*=7.1 Hz, 2H, CH_2), 3.21 (t, *J*=7.1 Hz, 2H, CH_2), 3.83 (s, 3H, CH_3, OMe), 5.21 (s, 1H pyrimidine), 5.72 (s, 1H, NH, D_2O exchangeable), 6.67-7.23 (m, 9H, Ar-H), 9.68, 9.74 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{21}H_{23}N_3O_2S$ (381.50): C, 66.12; H, 6.08; N, 11.01; S, 8.04 %. Found: C, 66.40; H, 6.32; N, 11.37; S, 8.25 %.

1-(6-Methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(4-acetophenylamino)-propan-1-one (3d)

Yield: 79 %. m.p. 190-192 °C. IR (KBr) ν (Cm^{-1}): 3442 (NH), 1681(C=O) 1220 (C=S). MS (EI) m/z: 419 (M^+, 81%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.23 (s, 3H, CH_3, pyrimidine), 2.50 (s, 3H, CH_3, C=OMe), 3.17 (t, *J*=7.1 Hz, 2H, CH_2), 3.29 (t, *J*=7.1 Hz, 2H, CH_2), 5.00 (d, *J*=7.2 Hz, 1H pyrimidine), 5.82 (s, 1H, NH, D_2O exchangeable), 6.19 (t, *J*=7.0 Hz, 1H, CH, CH=CH), 6.46 (d, *J*=7.0 Hz, 1H, CH, CH=CH), 7.2-7.4 (m, 9H, Ar-H), 9.51, 9. 62 (s, 2H, NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{24}H_{25}N_3O_2S$ (419.55): C, 68.71; H, 6.01; N, 10.02; S, 7.64 %. Found: C, 68.54; H, 6.32; N, 10.29; S, 7.42 %.

1-(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(4-acetophenylamino)-propan-1-one (3e)

Yield: 62 %. m.p. 260-262 °C. IR (KBr) ν (Cm^{-1}): 3374 (NH), 1694 (C=O) 1215 (C=S). MS (EI) m/z: 393 (M^+, 73 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.21 (s, 3H, CH_3), 2.45 (s, 3H, CH_3, C= OMe), 3.26 (t, *J*=7.3 Hz, 2H, CH_2), 3.31 (t, *J*=7.3 Hz, 2H, CH_2), 5.01 (s,1H pyrimidine), 5.74 (s, 1H, NH, D_2O exchangeable), 7.63 (dd, *J*=8.1 Hz, 4H, Ar-H), 7.23-7.33 (m, 5H, Ar-H), 9.42, 9.91 (s, 2H,NH, Pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{22}H_{23}N_3O_2S$ (393.51): C, 67.15; H, 5.89; N, 10.68; S, 8.15 %. Found: C, 67.35; H, 5.52; N, 10.39; S, 8.00 %.

1-(6-Methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(4-acetophenylamino)-propan-1-one (3f)

Yield: 60 %. m.p. 240-242 °C. IR (KBr) ν (Cm^{-1}): 3355 (NH), 1682 (C=O) 1199 (C=S). MS (EI) m/z: 423 (M^+, 85 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.26 (s, 3H, CH_3, pyrimidine), 2.47 (s, 3H, CH_3, C=OMe), 3.25 (t, *J*=7.1 Hz, 2H, CH_2), 3.42 (t, *J*=7.1 Hz, 2H, CH_2), 3.72 (s, 3H, CH_3, OMe), 5.21 (s, 1H, pyrimidine), 5.72 (s, 1H, NH, D_2O exchangeable), 6.73, 7.72 (m, 8H, Ar-H), 9.68, 9.73 (s, 2H, NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{23}H_{25}N_3O_3S$ (423.54): C, 65.23; H, 5.95; N, 9.92; S, 7.57 %. Found: C, 65.52; H, 5.74; N, 9.63; S, 7.24 %.

General procedure for preparation of compound 4

A mixture of pyrimidine derivatives 1a-c (0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in 10 % ethanolic sodium hydroxide solution (50 mL) was stirred at room temperature for 24 hours. The mixture was then heated under reflux for one hour, cooled, poured onto ice-water (100 mL) and acidified with conc. HCl (0.5 mL). The formed precipitate was filtered off, dried and recrystallized from aqueous DMF to give compounds 4a-f.

3-(4-Clorophenyl)-1-(6-methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-prop-2-en-1-one (4a)

Yield: 97 %. m.p. 252-254 °C. IR (KBr) ν (Cm^{-1}): 3420 (NH), 1689 (C=O) 1216 (C=S). MS (EI) m/z: 394 (M^+ , 3.7 %), 396 (M+2, 1.2 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.31 (s, 3H, CH_3, pyrimidine), 5.00 (dd, *J*=8.1 Hz, 2H, CH=CH), 5.06 (d, *J*=7.1 Hz, 1H pyrimidine), 6.51 (t, *J*=7.1 Hz, IH, CH, CH=CH), 6.72 (d, t, *J*=7.1 Hz, 1H, CH, CH=CH), 7.33-7.68 (m, 9H, Ar-H), 9.66, 10.42 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{22}H_{19}ClN_2OS$ (394.93): C, 66.91; H, 4.85; N, 7.09; S, 8.12; Cl, 8.98 %. Found: C, 66.70; H, 4.53; N, 6.99; S, 8.36; Cl, 8.80 %.

3-(4-Clorophenyl)-1-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-prop-2-en-1-one (4b)

Yield: 43 %. m.p. 285-287 °C. IR (KBr) ν (Cm^{-1}): 3367 (NH), 1699 (C=O) 1200 (C=S). MS (EI) m/z: 368 (M^+, 24 %), 370 (M+2, 8 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.27 (s, 3H, CH_3, pyrimidine), 4.99 (s, 1H pyrimidine), 5.01 (dd, *J*=8.1 Hz, 2H, CH=CH), 7.26-7.68 (m, 9H, Ar-H), 9.8, 10.02 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{20}H_{17}ClN_2OS$ (368.89): C, 65.12; H, 4.65; N, 7.59; S, 8.69; Cl, 9.61 %. Found: C, 65.40; H, 4.33; N, 7.39; S, 8.84; Cl, 9.40 %.

3-(4-Clorophenyl)-1-(6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-prop-2-en-1-one (4c)

Yield: 60 %. m.p. 195-197°C. IR (KBr) ν (Cm^{-1}): 3450 (NH), 1681 (C=O), 1195 (C=S). MS (EI) m/z: 398 (M^+ , 16.34 %), 400 (M+2, 5.2 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.27 (s, 3H, CH_3, pyrimidine), 3.81 (s, 3H, CH_3, OMe), 5.00 (s, 1H pyrimidine), 5.02 (dd *J*=8.1 Hz, 2H, CH=CH), 7.44-7.68 (m, 8H, aromatic), 9.80, 10.23 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{21}H_{19}ClN_2O_2S$ (398.91): C, 63.23; H, 4.80; N, 7.02; S, 8.04; Cl, 8.89 %. Found: C, 63.50; H, 4.57; N, 7.31; S, 8.26; Cl, 8.67 %.

3-(2-Methoxyphenyl)-1-(6-methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-prop-2-en-1-one (4d)

Yield: 75 %. m.p. 148-150 °C. IR (KBr) ν (Cm^{-1}): 3399 (NH), 1688 (C=O) 1207 (C=S). MS (EI) m/z: 390 (M^+ , 5.2 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.46 (s, 3H, CH_3, pyrimidine), 3.83 (s, 3H, CH_3, OMe), 4.95 (d, *J*=7.5 Hz, 1H pyrimidine), 5.09 (dd, *J*=8.1 Hz, 2H, CH=CH), 6.19 (t, *J*=7.5 Hz, 1H, CH, CH=CH), 6.5 (d, *J*=7.5 Hz, 1H, CH, CH=CH), 6.94-7.69 (m, 9H, aromatic), 9.68, 9.73 (s, 2H,

2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{23}H_{22}N_2O_2S$ (390.51): C, 70.74; H, 5.68; N, 7.17; S, 8.21 %. Found: C, 70.44; H, 5.39; N, 7.49; S, 8.44 %.

3-(2-Methoxyphenyl)-1-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-prop-2-en-1-one (4e)

Yield: 85 %. m.p. 240-242 °C. IR (KBr) ν (Cm^{-1}): 3403 (NH), 1749 (C=O) 1200 (C=S). MS (EI) m/z: 364 (M^+, 83 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.37 (s, 3H, CH_3, pyrimidine), 3.75 (s, 3H, CH_3, OMe), 4.99 (s, 1H pyrimidine), 5.5 (dd, *J*=6.9 Hz, 2H, CH=CH), 6.83-7.67 (m, 9H, Ar-H), 9.65, 9.83 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{21}H_{20}N_2O_2S$ (364.47): C, 69.21; H, 5.53; N, 7.69; S, 8.80 %. Found: C, 69.00; H, 5.38; N, 7.45; S, 8.59 %.

3-(2-Methoxyphenyl)-1-(6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-prop-2-en-1-one (4f)

Yield: 64 %. m.p. 145-147 °C. IR (KBr) ν (Cm^{-1}): 3357 (NH), 1696 (C=O) 1221 (C=S). MS (EI) m/z: 394 (M^+, 23 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.26 (s, 3H, CH_3, pyrimidine), 3.73 (s, 3H, CH_3, OMe), 3.63 (s, 3H, CH_3, OMe), 5.52 (dd, *J*=6.9 Hz, 2H, CH=CH), 5.25 (s, 1H pyrimidine), 6.94-7.64 (m, 8H, Ar-H), 10.05, 10.13 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{22}H_{22}N_2O_3S$ (394.50): C, 66.98; H, 5.62; N, 7.10; S, 8.13 %. Found: C, 66.98; H, 5.40; N, 7.31; S, 8.19 %.

General procedure for preparation of compound 5

To a solution of chalcone derivative 4a-f (0.01 mol) in dry ethanol (30 mL), phenyl hydrazine (4 mL) was first added, followed by glacial acetic acid (5 mL). The reaction mixture was heated under reflux for 5 hours, cooled, concentrated under reduced pressure; the precipitate formed was filtered, dried, and recrystallized from ethanol to give compounds 5a-f.

4-Styryl-6-methyl-5-(5-(4-clorophenyl)-1-phenyl-1H-pyrazol-3-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (5a)

Yield: 66 %. m.p. 110-112 °C. IR (KBr) ν (Cm^{-1}): 3470 (NH), 1608 (C=N) 1199 (C=S). MS (EI) m/z: 482 (M^+, 100 %), 484 (M+2, 31 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.32 (s, 3H, CH_3, pyrimidine), 5.21 (d, *J*=7.3 Hz, 1H pyrimidine), 6.35 (t, *J*=7.5 Hz, 1H, CH, CH=CH), 6.76 (d, *J*=7.3 Hz, 1H, CH, CH=CH), 7.24-7.98 (m, 15H, Ar-H), 10.10, 10.62 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for: C, 69.62; H, 4.80; N, 11.60; S, 6.64, Cl, 7.34 %. Found: C, 69.40; H,4.50; N, 11.37; S, 6.49; Cl, 7.66 %.

4-Styryl-6-methyl-5-(5-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (5b)

Yield: 70 %, m.p. 120-122 °C. IR (KBr) ν (Cm^{-1}): 3462 (NH), 1622(C=N) 1215 (C=S). MS (EI) m/z: 478 (M^+, 64.74 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.33 (s, 3H, CH_3, pyrimidine), 3.84 (s, 3H, CH_3, OCH_3), 5.23 (d, *J*=7.1 Hz, 1H pyrimidine), 6.21 (t, *J*=7.3 Hz, 1H, CH, CH=CH), 6.82 (d, *J*=7.3 Hz, 1H, CH, CH=CH), 7.05-8.32 (m, 15H, Ar-H), 9.60, 10.40 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{29}H_{26}N_4OS$ (478.62): C, 72.78; H, 5.48; N, 11.71; S, 6.70 %. Found: C, 72.54; H, 5.52; N, 11.93; S, 6.88 %.

4-Phenyl-6-methyl-5-(5-(4-clorophenyl)-1-phenyl-1H-pyrazol-3-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (5c)

Yield: 63 %. m.p. 225-227 °C. IR (KBr) ν (Cm^{-1}): 3475 (NH), 1595(C=N) 1211 (C=S). MS (EI) m/z: 456 (M^+, 68.29 %), 458 (M+2, 22.8 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.20 (s, 3H, CH_3, pyrimidine), 5.41 (s, 1H, pyrimidine), 7.23-7.98 (m, 15H, Ar-H), 10.31, 10.42 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{26}H_{21}ClN_4S$ (457.00): C, 68.33; H, 4.63; N, 12.26; S, 7.02; Cl, 7.76 %. Found: C, 68.65; H, 4.45; N, 12.54; S, 7.34; Cl, 7.36 %.

4-Phenyl-6-methyl-5-(5-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (5d)

Yield: 60 %. m.p. 185-187 °C. IR (KBr) ν (Cm^{-1}): 3393 (NH), 1622(C=N) 1216 (C=S). MS (EI) m/z: 452 (M^+, 58.35 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.30 (s, 3H, CH_3, pyrimidine), 3.80 (s, 3H, CH_3, OCH_3), 5.09 (s, 1H, pyrimidine), 7.07-8.22 (m, 15H, Ar-H), 9.73, 9.82 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{27}H_{24}N_4OS$ (452.58): C, 71.66; H, 5.35; N, 12.38; S, 7.08 %. Found: C, 71.83; H, 5.66; N, 12.00; S, 7.32 %.

4-(4-Methoxyphenyl)-6-methyl-5-(5-(4-clorophenyl)-1-phenyl-1H-pyrazol-3-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (5e)

Yield: 88 %. m.p. 200-202 °C. IR (KBr) ν (Cm^{-1}): 3458 (NH), 1601(C=N) 1199 (C=S). MS (EI) m/z: 486 (M^+, 13.33 %), 488 (M+2, 5 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.33 (s, 3H, CH_3, pyrimidine), 3.93 (s, 3H, CH_3, OCH_3), 5.51 (s, 1H Pyrim), 6.82-7.89 (m, 14H, Ar-H), 9.73, 10.53 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{27}H_{23}ClN_4OS$ (487.03): C, 66.59; H, 4.76; N; 11.50; S, 6.58; Cl, 7.28 %. Found: C, 66.29; H, 4.98; N, 11.29; S, 6.63; Cl, 7.60 %.

4-(4-Methoxyphenyl)-6-methyl-5-(5-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-1,2,3,4-tetrahydro pyrimidine-2(1H)-thione (5f)

Yield: 92 %, m.p. 130-132 °C. IR (KBr) ν (Cm^{-1}): 3479 (NH), 1599(C=N) 1223 (C=S). MS (EI) m/z: 482 (M^+, 85.90 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.26 (s, 3H, CH_3, pyrimidine), 3.63 (s, 3H, CH_3, OCH_3), 3.83 (s, 3H, CH_3, OCH_3), 5.02 (s, 1H pyrimidine), 7.07-8.32 (m, 14H, Ar-H), 10.02, 10.31 (s, 2H, 2NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{28}H_{26}N_4O_2S$ (482.61):C, 69.69; H, 5.43; N, 11.61; S, 6.64 %. Found: C, 69.39; H, 5.60; N, 11.84; S, 6.34 %.

General procedure for preparation of compound 6

To a solution of thiourea (0.76 g, 0.01 mol), in ethanol (20 mL), conc. HCl (5 mL) was added, then equimolar amount of appropriate chalcone 4a-f was added and the mixture was heated under reflux for 12 hours. The reaction mixture was concentrated to half its volume, cooled, neutralized with 25 % ammonium hydroxide solution (0.5 mL), and the precipitate formed was recrystallized from aqueous DMF to give compounds 6a-f.

6-(4-Clorophenyl)-4-(4-styryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-pyrimidine-2(1H)-thione (6a)

Yield: 63 %. m.p. 125-127°C. IR (KBr) ν (Cm^{-1}): 3375 (NH), 3300 (NH), 1254 (C=S), 1260 (C=S). MS (EI) m/z: 450 (M^+, 71 %), 452 (M+2, 23 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.21 (s, 3H, CH_3, pyrimidine), 5.12 (d, J=7.5 Hz, 1H, pyrimidine), 5.6 (s, 1H, pyrimidine), 6.45 (t, J=7.5 Hz, 1H, CH, CH=CH), 6.62 (d, J=7.5 Hz, 1H, CH, CH=CH), 7.32-7.44 (m, 9H, Ar-H), 9.05, 10.30, 10.31 (s, 3H, 3NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{23}H_{19}ClN_4S_2$ (451.02): C, 61.25; H, 4.25; N, 12.42; S, 14.22; Cl, 7.86 %. Found: C, 61.00; H, 4.50; N, 12.82; S, 14.47; Cl, 7.98 %.

6-(2-Methoxyphenyl)-4-(4-styryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-pyrimidine-2(1H)-thione (6b)

Yield: 65 %. m.p. 170-172 °C. IR (KBr) ν (Cm^{-1}): 3421 (NH), 3399 (NH), 1200 (C=S), 1198 (C=S). MS (EI) m/z: 446 (M^+, 24 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.26 (s, 3H, CH_3, pyrimidine), 3.81 (s, 3H, CH_3, OMe), 5.30 (d, *J*=8.1 Hz, 1H, pyrimidine), 5.41 (s, 1H, pyrimidine), 6.35 (t, *J*=7.5 Hz, 1H, CH, CH=CH), 6.84 (d, *J*=7.5 Hz, 1H, CH, CH=CH), 6.94-7.48 (m, 9H, Ar-H), 9.63, 10.62, 10.72 (s, 3H, 3NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{24}H_{22}N_4OS_2$ (446.60): C, 64.55; H, 4.97; N, 12.55; S, 14.36 %. Found: C, 64.32; H, 4.66; N, 12.78; S, 14.27 %.

6-(4-Clorophenyl)-4-(4-phenyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-pyrimidine-2(1H)-thione (6c)

Yield: 81 %. m.p. 205-207°C. IR (KBr) ν (Cm^{-1}): 3385 (NH), 3402 (NH), 1221 (C=S), 1233 (C=S). MS (EI) m/z: 424 (M^+, 82 %), 426 (M+2, 27 %).^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.23 (s, 3H, CH_3, pyrimidine), 5.13 (s, 1H, pyrimidine), 5.3 (s, 1H, pyrimidine), 7.26-7.49 (m, 9H, Ar-H), 9.62, 9.75, 10.24 (s, 3H, 3NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{21}H_{17}ClN_4S_2$ (424.98): C, 59.35; H, 4.03; N, 13.18; S, 15.09; Cl, 8.34 %. Found: C, 59.56; H, 4.21; N, 13.00; S, 15.23; Cl, 8.60 %.

6-(2-Methoxyphenyl)-4-(4-phenyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-pyrimidine-2(1H)-thione (6d)

Yield: 98 %. m.p. 190-192 °C. IR (KBr) ν (Cm^{-1}): 3178 (NH), 3321 (NH), 1210 (C=S), 1229 (C=S). MS (EI) m/z: 420 (M^+, 37 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.32 (s, 3H, CH_3, pyrimidine), 3.42 (s, 3H, CH_3, OMe), 5.00 (s, 1H, pyrimidine), 5.14 (s, 1H, pyrimidine), 6.94-7.33(m, 9H, Ar-H), 9.64, 9.73, 10.05 (s, 3H, 3NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{22}H_{20}N_4OS_2$ (420.56): C, 62.83; H, 4.79; N, 13.32; S, 15.25 %. Found: C, 62.59; H, 4.97; N, 13.14; S, 15.50 %.

6-(4-Clorophenyl)-4-(4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-yl)-pyrimidine-2(1H)-thione (6e)

Yield: 71 %. m.p. 200-202 °C. IR (KBr) ν (Cm^{-1}): 3352 (NH), 1260 (C=S). MS (EI) m/z: 454 (M^+, 42.73 %), 456 (M+2, 14.3 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.31 (s, 3H, CH_3, pyrimidine), 4.00 (s, 3H, CH_3, OMe), 5.15 (s, 1H, pyrimidine), 5.6 (s, 1H, pyrimidine), 6.42-7.57 (m, 8H, Ar-H), 10.52, 10.91, 10.99 (s, 3H, 3NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{22}H_{19}ClN_4OS_2$ (455.00): C, 58.08; H, 4.21; N, 12.31; S, 14.09, Cl, 7.79 %. Found: C, 58.21; H, 4.45; N, 12.54; S, 14.11; Cl, 7.90 %.

6-(2-Methoxyphenyl)-4-(4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-yl)-pyrimidine-2(1H)-thione (6f)

Yield: 75 %. m.p. 150-152 °C. IR (KBr) ν (Cm^{-1}): 3366 (NH), 3351 (NH), 1223 (C=S), 1238 (C=S). MS (EI) m/z: 450 (M^+, 28 %). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.20 (s, 3H, CH_3, pyrimidine), 3.74 (s, 3H, CH_3, OMe), 3.81 (s, 3H, CH_3, OMe), 5.21 (s, 1H, pyrimidine), 5.35 (s, 1H, pyrimidine), 6.57-7.72 (m, 8H, Ar-H), 10.87, 10.93, 10.99 (s, 3H, 3NH, pyrimidine, D_2O exchangeable). Anal. Calcd. for $C_{23}H_{22}N_4O_2S_2$ (450.59): C, 61.31; H, 4.92; N, 12.43; S, 14.23 %. Found: C, 61.21; H, 4.69; N, 12.73; S, 14.12 %.

ANTI-INFLAMMATORY ACTIVITY

Animals

70 Adult male Sprague-Dawley rats (5 rats per group), weighing 150-170 g, were housed at cages in a temperature-controlled (25±1 °c) environment and provided free access to pelleted food and purified drinking water. The animal experiments described below comply with the ethical principles and guidelines for the care and use of laboratory animals adopted by the National Egyptian Community.

Assessment of Anti-Inflammatory Activity

Rat paw oedema assay was carried out according to Winter *et al.* [16] Prepared compounds (equimolar to the reference drug) were dissolved in DMSO and administrated subcutaneously. One hour later, paw oedema was induced by subplantar injection of 0.1 mL of 1% carrageenan (Sigma-Aldrich, St. Louis, USA) into the right hind paw. Paw volume was measured using a water plethysmometer (Basile, Comerio, Italy). The difference between the right and left paw volume was measured at 1, 2, 3 and 4 h after induction of inflammation.

Control group (five rats per group) received DMSO subcutaneously and carrageenan in subplantar region. Results were expressed as percentage inhibition of inflammation. Ibuprofen (70 mg kg^{-1}) was used as the reference drug [17].

Statistical Analysis

Results are expressed as the mean ± SEM, and different groups were compared using one way analysis of variance (ANOVA) followed by Tukey-Kramer test for multiple comparisons, using Graph Pad instate (version 3.05) as the statistical software to calculate the statistics (Table 1).

RESULTS AND DISCUSSION

From the data shown in Table 1, it could be inferred that: Compounds 2a, 2c, 2f, 2i, 3c, 3e, 3f, 5b induced strong anti-inflammatory activity, comparable with that of ibuprofen (2a, 2c, 2f, 2i, 3c, 3f, 5b were significantly difference at 4 h post-carageenan to ibuprofen) and 2i, 3f, 3e have the same activity profile as ibuprofen (response increase by time). Compounds 1c, 2a, 2c, 2e, 3f, 4c, 6b, 6e, and 6f exerted good anti-inflammatory activity than ibuprofen at 3 h interval post-carageenan range from 65-81 %. Compounds 2a, 2c, 2i, 3c, 3f, 5b, 5f, 6b, 6f showed higher anti-inflammatory activities than ibuprofen at 1 hr interval post-carageenan range from 22-77 %. Compounds 1b, 1c, 2e, 3a, 4c, 4d, 4e, 6c showed no anti-inflammatory activity at 1st and 2nd hours interval post-carageenan. Yet, they exerted moderate anti-inflammatory activities at 4 h post-carageenan. Compound 1a had no anti-inflammatory activity at 1 h post-carageenan and showed moderate anti-inflammatory activity at 2nd, 3rd and 4th hours post-carageenan.

To analyze the structure-activity relationships we noticed that presence of p-methoxy phenyl group at C-4 plays an important role in the activity of compounds 2c, 2f, 2i, 3c, 3f that is the presence of p-methoxy phenyl group at C-4 enhances the anti-inflammatory activity. Further it is observed that the presence of p-methoxyphenyl group at C-4 and p-acetophenyl group in the side chain at C-5 together resulted in an excellent inhibition of inflammation (78, 86 %) in the 4th hour post-carageenan in compounds 2f, 3f. The presence of these groups may be making these compounds favourable electronically and stereochemically for interaction with the active site and thus exhibiting good anti-inflammatory activity.

CONCLUSION

We have synthesized a new series of thiopyrimidine derivatives and tested them for their anti-inflammatory activity.

Compounds 4-aryl-6-methyl-5(1-(arylimino)ethyl)-1,2,3,4-tetrahydropyrimidine-2-(*1H*)-thiones 2a, 2c, 2f, 2i, 1-(4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(arylamino) propan-1-ones 3c, 3f and 6-methyl-4-styryl-5-(5-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl)-1,2,3,4-tetrahydropyrimidine-2-(1*H*)-thione (5b) showed improved anti-inflammatory activity comparable to ibuprofen, while 1-(4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-ethanones 1a, 1b, 1c, 6-methyl-4-phenyl-5-(1-(4-acetophenyl-imino)ethyl)-1,2,3,4-tetrahydro pyrimidine-2-(*1H*)-thione (2e), 1-(6-methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-3-(phenylamino)-propan-1-one (3a), 3-aryl-1-(4-aryl-6-methyl-

2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-yl)-prop-2-en-1-one 4c, 4d, 4e, 4-(4-methoxyphenyl)-6-methyl-5-(5-(2-methoxyphenyl)-1-phenyl-*1H*-pyrazol-3-yl)-1,2,3,4-tetrahydropyrimidine-2-(*1H*)-thione (5f) and 6-aryl-4-(4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)-pyrimidine-2-(*1H*)-thiones 6b, 6c, 6e, 6f were either inactive or weakly active as anti-inflammatory agents.

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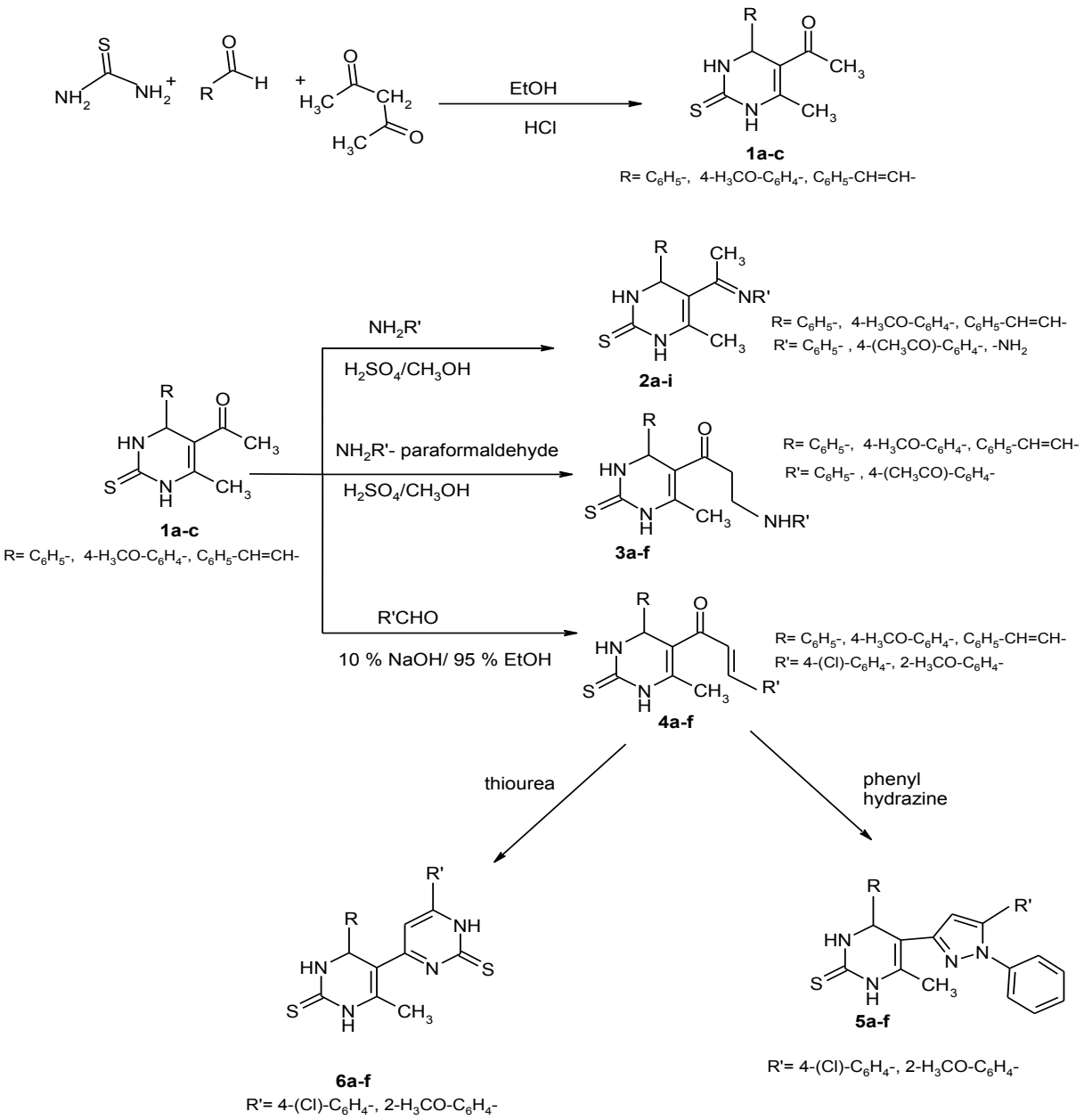

Scheme 1: Synthesis of Compounds 1a-c- 6a-f

Table 1: In Vivo Anti-Inflammatory Activity

Compounds	Edema induced by carrageenan (% edema inhibition relative to control)[a]			
	1h	2h	3h	4h
	mean ± SE (% inh.)	mean ± SE (% inh.)	mean ± SE (% inh.)	mean ± SE (% inh.)
1a	0.23 ± 0.007 (-)	0.17 ± 0.037 (35)	0.41 ± 0.037 (30)	0.30 ± 0.10 (53)
1b	0.24 ± 0.007 (-)	0.27 ± 0.002 (-)	0.44 ± 0.047 (19)	0.24 ± 0.124 (62)
1c	0.26 ± 0.024 (-)	0.26 ± 0.005 (-)	0.14 ± 0.093 (75)	0.25 ± 0.067 (61)
2a	0.11 ± 0.031 (53)	0.195 ± 0.048 (25)	0.187 ± 0.080 (65)	0.18 ± 0.081 (72**)
2c	0.12 ± 0.025 (46)	0.15 ± 0.042 (42)	0.19 ± 0.033 (65)	0.13 ± 0.033 (79***)
2e	0.24 ± 0.008 (-)	0.26 ± 0.003 (-)	0.19 ± 0.104 (65)	0.32 ± 0.057 (50)
2f	0.23 ± 0.026 (-)	0.27 ± 0.003 (-)	0.24 ± 0.107 (56)	0.14 ± 0.046 (78***)
2i	0.17 ± 0.035 (22)	0.16 ± 0.039 (35)	0.25 ± 0.072 (54)	0.17 ± 0.072 (73***)
3a	0.23 ± 0.002 (-)	0.26± 0.003 (-)	0.44± 0.014 (19)	0.41 ± 0.048 (35)
3c	0.05 ± 0.010 (77)	0.18 ± 0.049 (30)	0.31 ± 0.031 (42)	0.15 ± 0.055 (76***)
3e	0.23 ± 0.012 (-)	0.2 ± 0.035 (20)	0.23 ± 0.056 (56)	0.17 ± 0.136 (73)
3f	0.17 ± 0.043 (23)	0.17 ± 0.048 (33)	0.10 ± 0.012 (81)	0.08 ± 0.045 (86***)
4c	0.22 ± 0.002 (-)	0.26 ± 0.008 (-)	0.13 ± 0.035 (76)	0.31 ± 0.085 (51**)
4d	0.24 ± 0.007 (-)	0.26 ± 0.009 (-)	0.3 ± 0.053 (44)	0.23 ± 0.077 (63)

4e	0.22 ± 0.003 (-)	0.26 ± 0.003 (-)	0.44 ± 0.093 (20)	0.33 ± 0.091 (47)
5b	0.06 ± 0.021 (71)	0.132 ± 0.025 (49)	0.299 ± 0.005 (45)	0.132 ± 0.048 (79***)
5f	0.09 ± 0.027 (57)	0.18 ± 0.002 (27)	0.23 ± 0.060 (58)	0.24 ± 0.060 (61**)
6b	0.126 ± 0.028 (45)	0.195 ± 0.058 (25)	0.184 ± 0.055 (66)	0.233 ± 0.052 (63**)
6c	0.25 ± 0.002 (-)	0.26 ± 0.003 (-)	0.47 ± 0.087 (14)	0.37 ± 0.093 (42)
6e	0.25 ± 0.022 (-)	0.078 ± 0.024 (7)	0.15 ± 0.082 (71)	0.226 ± 0.046 (64)
6f	0.131 ± 0.022 (43)	0.223 ± 0.027 (14)	0.163 ± 0.049 (70)	0.3 ± 0.012 (51)
Ibuprofen	0.216 ± 0.032 (6)	0.14 ± 0.055 (45)	0.214 ± 0.019 (60)	0.192 ± 0.015 (69*)
control	0.23 ± 0.033 (-)	0.26 ± 0.037 (-)	0.544 ± 0.08 (-)	0.63 ± 0.03 (-)

- [a] solvent: 2.5 mL DMSO. Dose: 70 mg kg^{-1} ibuprofen and the equivalent amount of tested compounds.
- Control (DMSO) has no anti-inflammatory activity.
- %inhibition =(1-rt/rc)x100 [rt= mean of tested group; rc= mean of control group]
- *Significantly different compared to control at respective time point at $p < 0.05$
- **Significantly different compared to ibuprofen at respective time point at $p < 0.05$

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