Indian Journal of Chemistry
Vol. 49B, February 2009, pp. 273-281

Synthesis, anti-inflammatory and analgesic activity evaluation of some pyrimidine derivatives

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Received 10 June 2008; accepted (revised) 10 December 2008

A number of pyrimidine derivatives **1-3, 5-19** have been synthesized by condensation of bis(2-(vinyloxy))ethylamine, cyclopropylamine, *N*-(2-amino-4-ethoxyphenyl)acetamide, 2-(aminomethyl thiophene), 2-thiophen ethylamine, 2-hydrazinopyridine, 1-aminonaphthalen-2-ol hydrochloride, furfuryl amine, 2-(4-imidazolyl)ethylamine, 2-picolylamine and 4-methoxyl-2-nitroaniline with various isothiocyanatoketones. These compounds have been screened for anti-inflammatory and analgesic activities. Compounds **10** and **14** have exhibited 40% and 39% anti-inflammatory and compound **11** has showed 75% analgesic activity at 100 mg/kg p.o. respectively.

Keywords: Pyrimidines, carrageenan, anti-inflammatory, analgesic

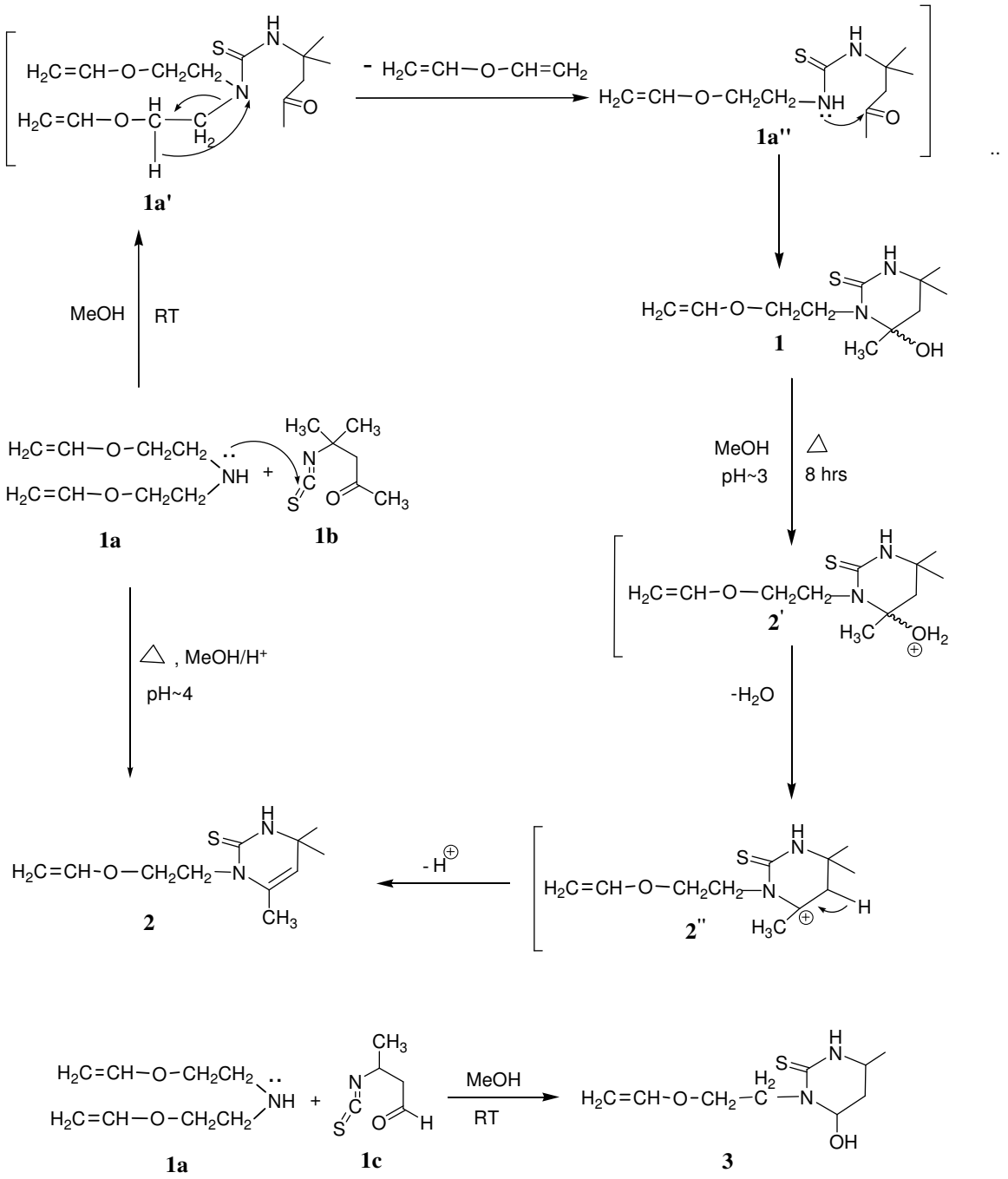
Inflammatory diseases like arthritis, allergy, asthma, multiple sclerosis etc. are quite common and need a considerable attention. Literature survey reveals that vast amount of research is going on in search of safer anti-inflammatory drugs. Pyrimidine derivatives are biologically interesting molecules that have established utility for the treatment of Alzheimer's disease[1] and proliferative disorders[2,3]. They are also capable of showing antiviral activity[4,5], act as anti-HIV agents[6], as antihypertensive agents[7], antimicrobial agents[8,9] and as fungicides[10]. Along with these activities numerous research papers have shown that pyrimidine derivatives have other diverse pharmacological activities such as they act as H_1-antihistamines[11], as selective type 4 phosphodiesterase inhibitors[12] and as anti-inflammatory agents[13-18]. Tempted by wide range of biological activities exhibited by pyrimidine derivatives and in continuation of our efforts[19-22] in search of potent molecules possessing anti-inflammatory and analgesic activities, a wide variety of pyrimidine derivatives are synthesized and evaluated for anti-inflammatory and analgesic activities.

Results and Discussion

Bis(2-(vinyloxy)ethyl)amine **1a** (**Scheme I**) on condensation with 4-isothiocyanato-4-methyl pentan-2-one[23] gave condensed product **1** (**Scheme I**). Spectral and analytical data of **1** reported in experimental section is in agreement with the structure assigned to it. Formation of **1** can be explained (**Scheme I**) by nucleophilic attack of –NH- of **1a** on isothiocyanato group of **1b** giving a non isolable thiourea intermediate **1a′**. From **1a′**, there is loss of neutral bisvinyloxy moiety resulting in formation of **1a″** (**Scheme I**) and further nucleophilic attack of –NH- on -CO- group afforded cyclized product **1**. When compound **1** was heated under reflux for 8 hr using methanol as a solvent at *p*H ~3, dehydrated product **2** (**Scheme I**) was obtained *via* non isolable intermediates **2′** and **2″**. Spectral and analytical data reported in experimental section fully support the structure assigned to compound **2**.

A comparison of ^{1}H NMR of **1** and **2** indicates absence of signals at δ: 1.88-1.98 (m, 2H, -CH_2- of pyrimidine) and 5.81-5.83 (d, 1H, OH, D_2O exchangeable) in the ^{1}H NMR of **2** and presence of a signal at δ: 4.77 (s, 1H, =CH-) in the ^{1}H NMR of **2**. These observations confirm elimination of H_2O from **1** leading to the formation of **2**.

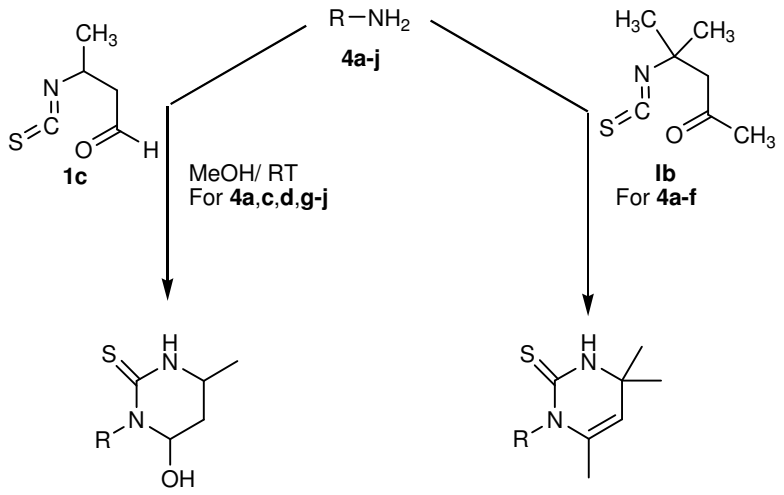
Direct condensation of **1a** with **1b** using methanol as solvent, adjusting *p*H ~4-5 and heating under reflux, on usual work=up gave compound **2**. The yield of product **2** obtained by direct condensation was slightly more than what was obtained by dehydration of **1** to **2**. Condensation of **1a** with



Scheme I

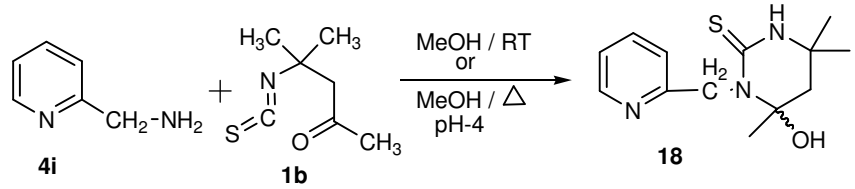
3-isothiocyanatobutanal (**1c**, **Scheme I**, ref.24) at RT gave product **3** in good yield. Spectral and analytical data of **3** reported in experimental section is in complete agreement with the structure assigned to it. In an attempt to get dehydrated product of **3** by heating it under reflux in methanol after adjusting its *p*H ~3, we got only unidentifiable material.

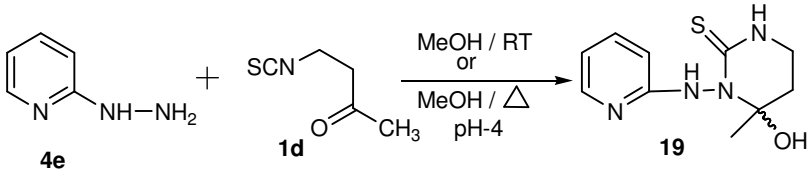
Condensation of cyclopropylamine (**4a**, **Scheme II**) with **1b** at RT using methanol as solvent of reaction gave dehydrated product **5** where as condensation of *N*-(2-amino-4-ethoxyphenyl)acetamide (**4b**, **Scheme II**) with **1b** at RT using acetic acid as solvent of reaction gave product **6** in 84% and 40% yield, respectively. Spectral and analytical data of **5** and **6** reported in experimental section is in agreement with the structures assigned to them. Condensation of 2-



11 R= cyclopropyl
12 R= 2-thienyl methyl
13 R= thienyl ethyl
14 R= 2-furyl methyl
15 R= imidazol-4-ethyl
16 R= 2-pyridyl methyl
17 R= 2-nitro-4-methoxy phenyl

5 R= cyclopropyl
6 R= 2-acetamido-4-ethoxyphenyl
7 R= 2-thienyl methyl
8 R= 2-thienyl ethyl
9 R= 2-pyridyl amino
10 R= 2-hydroxy-1-naphthyl





Scheme II

(aminomethyl) thiophene **4c**, 2-thiophene ethylamine **4d**, 2-hydrazino pyridine **4e** and 1-amino naphthalene-2-ol hydrochloride **4f** with **1b** by heating under reflux in methanol after adjusting the *p*H of reaction=mixture ~4 (by adding a few drops of 10% sulphuric acid in methanol) gave products **7-10** respectively. Structures assigned to **7-10** (**Scheme II**) are fully supported by spectral and analytical data reported in experimental section. Cyclopropyl amine **4a**, 2-(aminomethyl)thiophene **4c**, 2-thiophene ethylamine **4d**, furfuryl amine **4g**, 2-(4-imidazolyl) ethylamine **4h**, 2-picolyl-amine **4i** and 4-methoxy-2-nitro aniline **4j** on condensation with 3-isothiocyanatobutanal **Ic** at RT using methanol as solvent of reaction gave products **11-17** (**Scheme II**) respectively. Structures of products **11-17** are confirmed by the spectral and analytical data reported in the experimental section.

2-Picolylamine **4i** on condensation with **1b** gave **18** (**Scheme II**) in good yield. When it was tried to synthesize dehydrated product of **18** i.e. 4,4,6 trimethyl-1-(pyridine-2-ylmethyl)-3,4-dihydropyrimidine-2(1*H*) thione by heating compound 18 in methanol under reflux for eight hr at *p*H ~3, it was observed that no dehydrated product was formed and only starting material i.e. **18** was recovered back. Even direct condensation of **4i** with **1b** using methanol as solvent, adjusting *p*H ~4 and heating

under reflux, on usual work=up did not give dehydrated product, rather only hydrated product **18** was obtained.

Condensation of 2-hydrazinopyridine **4e** with 4-isothiocyanatobutane-2-one **1d** gave product **19**. Spectral data of **18** and **19** reported in experimental section fully support the structures assigned to them. It was observed that when experiments were tried to obtain the dehydrated products of **11-17** and **19** by refluxing each of them at *p*H ~3 in methanol as a solvent, rather than getting dehydrated products, only unidentifiable materials were obtained.

Biological results

Compounds **1-3**, **5-8**, **10-16** and **18-19** at 100 mg/kg po were tested for anti-inflammatory activity in the carrageenin-induced paw oedema model[25] and results are summarized in **Table I**. Compounds **1-3**, **5-8**, **10-16** and **18-19** showed 9%, 0%, 0%, 17%, 24%, 0%, 16%, 40%, 21%, 2%, 7%, 39%, 7%, 0%, 0%, and 2% anti-inflammatory activity respectively, whereas standard drug ibuprofen exhibited 68% activity at 100 mg/kg po. Compounds **1-3**, **5-8**, **10-19** on analgesic activity evaluation at 100 mg/kg po using writhing assay[26] (**Table I**) exhibited 50%, 50%, 50%, 25%, 50%, 25%, 25%, 25%, 75%, 25%, 25%, 50%, 50%, 50%, 25%, 25% and 50% analgesic activity respectively, whereas ibuprofen exhibited 75% and 50% analgesic activity at 100 mg/kg po and 50 mg/kg po respectively. Compound **11** also exhibited 50% analgesic activity at 50 mg/kg po. Analgesic activity of compound **11** is comparable to ibuprofen. It is observed that although all the compounds contain pyrimidine moiety but compounds **10** and **14** showed good anti-inflammatory activity i.e., 40% and 39% at 100 mg/kg po, this is because of hydroxy naphthyl group (in case of **10**) and methyl furan group (in case of **14**) being directly attached to first position N atom of pyrimidine ring, 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. In case of analgesic activity evaluation it is found that all the tested compounds though contains same pyrimidine moiety but only compounds **11** (75% at 100 mg/kg po) showed good analgesic activity. It is possible that attachment of cyclopropyl group to first position N atom of pyrimidine ring may make it suitable stereochemically to interact with the active site and thus exhibiting good analgesic activity.

In conclusion various pyrimidine derivatives **1-3**, **5-8**, **10-19** have been synthesized and screened for anti-inflammatory and analgesic activities. Compounds **10** and **14** exhibited good anti-inflammatory activity and compound **11** exhibited good analgesic activity.

Table I—Anti-inflammatory and analgesic activity evaluation of compounds **1-3**, **5-8**, **10-19**

Compds tested	Dose mg/kg p.o	Anti-inflammatory %	Analgesic %
1	100	9.0	50
2	100	0.0	50
3	100	0.0	50
5	100	17	25
6	100	24	50
7	100	0.0	25
8	100	16	25
10	100	40	25
11	100	21	75
	50	-	50
12	100	2	25
13	100	7	25
14	100	39	50
15	100	7	50
16	100	0.0	50
17	100	-	25
18	100	0.0	25
19	100	2	50
Ibuprofen	100	68	75
	50	38	50

Experimental Section

Melting points were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 FT spectrometer. ^{1}H NMR were recorded on a Bruker WH-300/Bruker av-500 spectrometer in a *ca.* 5-15% (w/v) solution in appropriate deuterated solvent. FAB-MS was recorded on a Jeol SX-120 (FAB) spectrometer. GC-MS was recorded using Clarus 500 gas chromatograph from Perkin-Elmer where built in MS detector was used. Thin-layer chromatography was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapours or by irradiation with UV light (254 nm). Column chromatography was performed by using Qualigens silica gel for column chromatography (60-120 mesh). Elemental analysis was performed using a Vario EL III elementar analyzer.

General procedure for room temperature reactions

4-Hydroxy-4, 6, 6-trimethyl-3-(2-(vinyloxy)ethyl)tetrahydro pyrimidine-2(1*H*)-thione 1

Bis(2-(vinyloxy)ethyl)amine **1a** (0.31 mL; 2 mmole) was taken in methanol (10 mL) and to it was added 4-isothiocyanato-4-methyl pentan-2-one (0.31 mL, 2 mmole). The reaction contents were allowed to stand at RT for two days. Solvent was allowed to evaporate at RT, the residue left behind was scratched with chilled methanol: diethyl ether (1:5) (5 mL). The solid separated out was filtered and washed with chilled methanol: ethyl acetate (1:1) to give pure condensed product **1**. Yield 0.410 g, 84%; m.p. 150°C; IR (KBr): 3501, 3400 (OH, NH), 1541, 1493, 1458 (Ar) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ 1.15 (s, 3H, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 1.46 (s, 3H, $-CH_3$), 1.88-1.98 (m, 2H, $-CH_2-$ of pyrimidine), 3.53-3.60 (m, 4H, 2 × $-CH_2-$), 3.72-3.78 (q, 1H, one H of $=CH_2$), 3.88-3.92 (m, 1H, one H of $=CH_2$); 3.99-4.04 (m, 1H, =CH-O-), 5.81-5.83 (d, 1H, OH, D_2O exchangeable), 8.19 (bs, 1H, NH, D_2O exchangeable), GC-MS does not show M^+ ion peak but gave other peaks which arose due to fragmentation of 1, i.e., *m/z* 183($C_9H_{15}N_2S$,1.61%), 182 ($C_9H_{14}N_2S$,14.80%); Anal. Calcd. for $C_{11}H_{20}N_2O_2S$: C, 54.09; H, 8.19; N, 11.47; S, 13.11. Found: C, 53.77; H, 8.50; N, 10.90; S, 13.55%.

Similarly compounds **5** and **18** were also synthesized.

1-Cyclopropyl-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione 5

Crystallised with MeOH; yield 84%; m.p. 155°C; IR (KBr): 3174 (NH), 1590, 1523 and 1454 (Ar) cm^{-1}: ^1H NMR (400 MHz, DMSO-d_6): δ 0.58-0.62 (m, 2H, $-CH_2-$), 0.94-0.99 (m, 2H, $-CH_2-$), 1.07 (s, 6H, 2 × $-CH_3$), 1.992-1.995 (d, 3H, $-CH_3$), 2.73 -2.76 (m, 1H, =CH-N=), 4.84-4.85 (t, 1H, =CH-), 8.64 (bs, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 196 (M^+, 45.55%); Anal. Calcd. for $C_{10}H_{16}N_2S$: C, 61.22; H, 8.16; N, 14.28; S, 16.32. Found: C, 61.01; H, 7.99; N, 13.98; S, 16.01%.

4-Hydroxy-4,6,6-trimethyl-3-(pyridin-2-ylmethyl)-tetrahydro pyrimidine-2(1*H*) thione 18

Crystallised with MeOH; yield 75%; m.p. 160°C; IR (KBr): 3227, 3415 (OH, NH), 1537 and 1473 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.23 (s, 3H, $-CH_3$), 1.32 (s, 3H, $-CH_3$), 1.35 (s, 3H, $-CH_3$), 1.97-2.00 (d, 1H, *J*=13.5 Hz, one H of pyrimidine $-CH_2-$), 2.04-2.07 (d, 1H, *J*=13.5 Hz,one H of pyrimidine $-CH_2-$), 5.08-5.11 (d, 1H, *J*=17.0 Hz, one H of $-CH_2$), 5.42-5.45 (d, 1H, *J*=17.0 Hz, one H of $-CH_2$), 6.49 (bs, 1H, OH, D_2O exchangeable), 7.20-7.23 (q, 1H, py), 7.30-7.32 (q, 1H, py), 7.71-7.75 (m, 1H, py), 8.39 (bs, 1H, NH, D_2O exchangeable), 8.45-8.46 (d, 1H, *J*=5.0Hz, py); GC-MS: *m/z* 247 (M^+- H_2O, 2.13%); Anal. Calcd. for $C_{13}H_{19}N_3OS$: C, 58.86; H, 7.16; N, 15.84; S, 12.07. Found: C, 58.49; H, 7.01; N, 15.70; S, 12.00%.

General procedure for *p*H adjusted reactions

i) First Procedure

4,4,6-Trimethyl-1-(2-(vinyloxy)ethyl)-3,4-dihydropyrimidine-2(1*H*)-thione 2

Bis(2-(vinyloxy)ethyl)amine (0.31 mL; 2 mmole) was taken in methanol (10 mL) and to it was added 4-isothiocyanato-4-methyl pentan-2-one (0.31 mL, 2 mmole). The *p*H of reaction contents was adjusted to ~4 by adding a few drops of 10% H_2SO_4 in methanol. The reaction-mixture was heated under reflux for 8 hr and then solvent was removed under reduced pressure. The residue left behind was treated with 10% sodium bicarbonate solution and the solid so obtained was filtered, washed with water, vaccum dried to give crude product which was crystallized from methanol to give pure product 2. Yield 0.330 g, 73%; m.p. 162°C; IR (KBr): 3212 (NH), 1680 (C=N), 1535 & 1447 (Ar) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.15 (s, 6H, 2 × $-CH_3$), 1.93 (s, 3H, $-CH_3$), 3.51-3.62 (m, 5H, =CH + 2 × CH_2), 4.20 (s, 2H, $=CH_2$), 4.77 (s, 1H, =CH-), 8.59 (bs, 1H, NH, D_2O exchangeable). GC-MS: *m/z* 226 (M^+, 0.81%); Anal. Calcd. for $C_{11}H_{18}N_2OS$: C, 58.40; H, 7.96; N, 12.38; S, 14.15. Found: C, 58.39; H, 7.59; N, 12.20; S, 14.00%.

Similarly compounds **7**, **8**, **9** and **10** were also synthesized.

ii) Second procedure

4,4,6-Trimethyl-1-(2-(vinyloxy)ethyl)-3,4-dihydropyrimidine-2(1*H*)-thione 2

Compound **1** was dissolved in methanol (10 mL) and the *p*H of the reaction-mixture was adjusted to ~3 by adding a few drops of 10% H_2SO_4 in methanol. The reaction contents were heated under reflux for 8 hr, solvent was removed under reduced pressure and the residue left behind was treated with 10% sodium bicarbonate solution (5 mL). The solid product so obtained was filtered, washed with water, dried under vaccum and crystallized from methanol to give pure product **2**. Yield 0.280 g, 62%. Compound **2** obtained

by above method and that obtained by direct condensation are found to be same but the yield is more in case of direct condensation.

4,4,6-Trimethyl-1-(thiophen-2-ylmethyl)-3,4-dihydropyrimidine-2(1*H*)-thione 7

Crystallized with MeOH; yield 89%; m.p. 160°C; IR (KBr): 3462, 3219 (NH), 1687 (C=N), 1526, 1450 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.16 (s, 6H, 2 × -CH_3), 1.90 (s, 3H, -CH_3), 4.82 (s, 1H, =CH-), 5.60 (s, 2H, –CH_2-), 6.95-6.97 (q, 1H, Ar), 7.00-7.01 (q, 1H, Ar), 7.38-7.40 (q, 1H, Ar), 8.73 (bs, 1H, NH, D_2O exchangeable); GC-MS: no M^+ peak but other fragmented peaks were observed i.e., *m/z* 155 ($C_7H_{11}N_2S^+$, 0.08%). 97 ($C_5H_5S^+$, 100%), 83 ($C_4H_3S^+$, 1.65%); Anal. Calcd. for $C_{12}H_{16}N_2S_2$: C, 57.14; H, 6.34; N, 11.1; S, 25.39. Found: C, 57.02; H, 6.23; N,10.98; S, 25.10%.

4,4,6-Trimethyl-1-(2-(thiophen-2-yl)ethyl)-3,4-dihydropyrimidine-2(1*H*)-thione 8

Crystallized with MeOH; yield 52%; m.p. 95°C; IR (KBr): 3470 (NH), 1640 (C=N), 1519, 1443, 1419 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.15 (s, 6H, 2 ×-CH_3), 1.87 (s, 3H, -CH_3), 3.13 (t, 2H, -CH_2-), 4.31 (s, 2H, -CH_2-), 4.77 (s, 1H, =CH-), 6.92-6.96 (m, 2H, Ar), 7.35 (dd, 1H, Ar), 8.63 (bs, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 266 (M^+; 13.06%); Anal. Calcd. for $C_{13}H_{18}N_2S_2$: C, 58.64; H, 6.76; N, 10.52; S, 24.06. Found: C, 58.47; H, 6.49; N, 10.45; S, 23.96%.

4,4,6-Trimethyl-1-(pyridin-2-ylamino)-3,4-dihydropyrimidine-2(1*H*)-thione 9

Solvent of elution: EtOAc: MeOH (8:2, v/v); yield 32%; m.p. 170°C; IR (KBr): 3219 (NH), 1680 (C=N), 1601, 1527 and 1471 (Ar) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.25 (s, 3H, -CH_3), 1.30 (s, 3H, -CH_3), 1.75 (s, 3H, -CH_3), 4.83 (s, 1H, =CH-), 6.53-6.55 (d, 1H, *J*=8.0 Hz, py), 6.74-6.77 (q, 1H, py), 7.54-7.59 (m, 1H, py), 8.07-8.08 (q, 1H, py), 8.61 (s, 1H, NH, D_2O exchangeable); 8.85 (s, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 248 (M^+, 0.99%); Anal. Calcd. For $C_{12}H_{16}N_4S$: C, 58.06; H, 6.45; N, 22.58; S, 12.90. Found: C, 57.94; H, 6.39; N, 22.46; S, 12.78%.

1-(2-Hydroxynaphthalen-1-yl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione 10

Solvent of elution: EtOAc: MeOH (9:1, v/v); yield 67%; m.p. 210°C; IR (KBr): 3192 (NH), 1541 and 1509 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.27 (s, 3H, -CH_3), 1.35 (s, 3H, -CH_3), 1.39 (s, 3H, -CH_3), 4.93 (s, 1H, =CH-), 7.18-7.19 (d, 1H, *J* = 8.5 Hz, Ar), 7.29 (s, 1H, Ar), 7.48 (s, 2H, Ar), 7.76-7.78 (d, 1H, *J*=8.5 Hz, Ar), 7.81-7.82 (d, 1H, *J*=8.0 Hz, Ar), 8.80 (s, 1H, OH, D_2O exchangeable), 9.95 (s, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 298 (M^+, 26.68%); Anal. Calcd. for $C_{17}H_{18}N_2OS$: C, 68.45; H, 6.04; N, 9.39; S, 10.70. Found: C, 68.35; H, 6.00; N, 9.18; S, 9.99%.

4-Hydroxy-6-trimethyl-3-(2-(vinyloxy)ethyl)-tetrahydropyrimidine-2(1*H*)-thione 3

Bis(2-(vinyloxy)ethyl)amine **1a** (0.31 mL; 2 mmole) was dissolved in MeOH (10 mL) and 3-isothiocyanatobutanal (0.26 mL; 2 mmole) was added to it. The reaction contents were allowed to stand at RT for two days. Solvent was allowed to evaporate at RT and the semi solid residue was dissolved in methanol. The resulting solution was adsorbed on silica gel and subjected to column chromatography over silica gel. Elution with $CHCl_3$: EtOAc (1:9, v/v) removed any side products and further elution with ethylacetate gave pure product 3; yield 0.370 g (85%); m.p. 145°C; IR (KBr): 3458, 3200 (NH, OH), 1536 and 1447 (Ar) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.12-1.13 (d, 3H, -CH_3), 1.40-1.46 (q, 1H, one H of pyrimidine -CH_2-), 1.83-1.87 (d, 1H, *J*=13.0 Hz, one H of pyrimidine -CH_2-), 3.57-3.75 (m, 4H, 2 × -CH_2-), 3.95-3.97 (m, 2H, -C*H*-CH_3 + OH, D_2O exchangeable), 4.11-4.12 (m, 1H, -C*H*-OH), 4.92-4.95 (m, 2H, =CH_2), 6.19-6.22 (m, 1H, =CH-O-), 8.15 (bs, 1H, NH, D_2O exchangeable). GC-MS: *m/z* 216 (M^+, 25.34%); Anal. Calcd. for $C_9H_{16}N_2O_2$ S: C, 50.00; H, 7.40; N, 12.96; S, 14.81%. Found: C, 49.92; H, 7.24; N, 12.57; S, 14.74%.

Similarly compounds **11-17** were also prepared.

3-Cyclopropyl-4-hydroxy-6-methyl-tetrahydropyrimidine-2(1*H*)-thione 11

Solvent of elution: $CHCl_3$: EtOAc (5:5, v/v); yield 78%; m.p. 135°C; IR (KBr): 3234 and 3100 (NH, OH),1528, 1483 and 1449 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.64-0.76 (m, 4H, -CH_2-CH_2-), 1.093-1.097 (d, 3H, *J*=2.0 Hz, -CH_3), 1.37-1.42 (m, 1H, one H of pyrimidine -CH_2-), 1.81-1.83 (d, 1H, *J*=10.0 Hz, one H of pyrimidine -CH_2-), 2.93-2.96 (m, 1H, CH_3-CH-N=), 3.51-3.53 (m, 1H, -C*H*-CH_3), 4.80-4.81 (t, 1H, -CH-OH), 6.05-6.06 (d, 1H, OH, D_2O exchangeable), 8.15 (bs, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 168 (M^+- H_2O, 54.62%);

Anal. Calcd. for $C_8H_{14}N_2OS$: C, 51.61; H, 7.52; N, 15.05; S, 17.20. Found: C, 51.35; H, 7.45; N, 14.75; S,16.93%.

4-Hydroxy-6-methyl-3-(thiophen-2-ylmethyl)-tetrahydropyrimidine-2(1*H*)-thione 12

Crystallization from EtOAc: MeOH (5:5, v/v); yield 82%; m.p. 140°C; IR (KBr): 3317, 3233 (OH, NH), 1534, 1494 and 1444 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.13-1.14 (d, 3H, *J*=6.5 Hz, -CH_3), 1.14-1.20 (m, 1H, one H of pyrimidine -CH_2-), 2.11-2.13 (dd, 1H, one H of pyrimidine -CH_2-), 3.30 (s, 1H, OH, D_2O exchangeable), 3.38-3.42 (m, 1H, -C*H*-CH_3), 4.50 (s, 1H, -C*H*-OH), 4.64-4.67 (d, 1H, *J*=15.5 Hz, one H of -CH_2-), 5.87-5.90 (d, 1H, *J*=15.0 Hz one H of -CH_2-), 6.96-6.97 (q, 1H, Ar), 7.11-7.12 (d, 1H, *J*=2.5 Hz, Ar), 7.41-7.42 (d, 1H, *J*=5.0 Hz, Ar), 8.48 (bs, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 224 (M^+-H_2O, 45.47%); Anal. Calcd. for $C_{10}H_{14}N_2OS_2$: C, 49.58; H, 5.78; N, 11.57; S, 26.44. Found: C, 49.34; H, 5.46; N, 11.23; S, 26.34%.

4-Hydroxy-6-methyl-3-(2-(thiophen-2-yl)ethyl)-tetrahydropyrimidine-2(1*H*)-thione 13

Solvent of elution: EtOAc: MeOH (9:1, v/v); yield 82%; m.p. 120°C; IR (KBr): 3370, 3200 (OH, NH), 1532, 1441 and 1373 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.07-1.08 (d, 3H, *J*=6.5 Hz, -CH_3), 1.35-1.38 (dd, 1H, one H of pyrimidine -CH_2-), 1.80-1.82 (d, 1H, *J*=13.0 Hz one H of pyrimidine -CH_2-), 3.16-3.22 (m, 2H, -CH-CH_3 + -CH-OH), 3.43-3.55 (m, 1H, one H of -CH_2-), 3.62-3.67 (m, 1H, one H of -CH_2-), 4.20-4.30 (m, 1H, one H of -CH_2-), 4.73-4.74 (t, 1H, one H of -CH_2-), 6.34-6.35 (d, 1H, -OH, D_2O exchangeable), 6.88-6.89 (d, 1H, *J*=2.5 Hz, Ar), 6.96-6.97 (q, 1H, Ar), 7.34-7.35 (d, 1H, *J*=4.5 Hz, Ar), 8.18 (s, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 238 (M^+-H_2O, 11.12%); Anal. Calcd. for $C_{11}H_{16}N_2OS_2$: C, 51.56; H, 6.25; N, 10.93; S, 25.00. Found: C, 51.23; H, 6.21; N, 10.35; S, 24.56%.

1-(Furan-2-ylmethyl)-6-hydroxy-4-methyl-tetrahydropyrimidine-2(1*H*)-thione 14

Crystallized from MeOH; yield 88%; m.p. 110°C; IR (KBr): 3216, 3098 (OH, NH), 1537, 1493 and 1452 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.13-1.15 (d, 3H, -CH_3), 1.18-1.19 (m, 1H, one H of pyrimidine -CH_2-), 2.13-2.15 (m, 1H, one H of pyrimidine -CH_2-), 3.41-3.46 (m, 2H,-CH-CH_3 + OH, D2O exchangeable), 4.52-4.55 (s + d, 2H, -CH-OH + one H of -CH_2-), 5.70-5.73 (d, 1H, *J*=15.5 Hz, one H of CH_2), 6.340-6.346 (d, 1H, *J*=3.0 Hz, Ar), 6.41-6.42 (t, 1H, Ar), 7.59 (s, 1H, Ar), 8.47 (bs, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 208 (M^+-H_2O, 81.43%); Anal. Calcd. for $C_{10}H_{14}N_2O_2S$: C, 53.09; H, 6.19; N, 12.38; S, 14.15. Found: C, 52.89; H, 6.10; N, 12.23; S, 14.02%.

3-(2-(1*H*-imidazol-4-yl)ethyl-4-hydroxy-6-methyl-tetrahydropyrimidine-2(1*H*)-thione 15

Solvent of elution: EtOAc: MeOH (8:2, v/v); yield 44%; m.p. 230°C; IR (KBr): 3300, 3239 (OH, NH), 1625 (C=N), 1502, 1448 and 1374 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.19-1.20 (d, 3H, *J*=6.5 Hz -CH_3), 1.88-1.90 (q, 1H, one H of pyrimidine -CH_2-), 2.20-2.23 (m, 1H, one H of pyrimidine -CH_2-), 2.82-2.86 (m, 1H, -C*H*-CH_3), 2.92 (bs, 1H, OH, D_2O exchangeable), 2.98-3.00 (m, 1H, -C*H*-OH), 3.29-3.34 (m, 2H, -CH_2-), 5.24-5.28 (m, 1H, one H of -CH_2-), 5.83-5.87 (m, 1H, one H of -CH_2-), 7.17 (s, 1H, Ar), 8.55 (s, 1H, Ar), 8.78 (bs, 1H, NH, D_2O exchangeable). Aromatic NH is expected downfield; GC-MS: *m/z* 222 (M^+-H_2O, 17.36%); Anal. Calcd. for $C_{10}H_{16}N_4OS$: C, 50.00; H, 6.66; N, 23.33; S, 13.33. Found: C, 49.78; H, 6.46; N, 23.14; S, 13.13%.

4-Hydroxy-6-trimethyl-3-(pyridin-2-ylmethyl)-tetrahydropyrimidine-2(1*H*)-thione 16

Solvent of elution: $CHCl_3$: EtOAc (1:9, v/v); yield 38%; m.p. 155°C; IR (KBr): 3445, 3317 (OH, NH), 1634 (C=N), 1597, 1522 and 1478 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.17-1.18 (d, 3H, *J*=6.4Hz, -CH_3), 1.52-1.59 (m, 1H, one H of pyrimidine CH_2-), 1.91-1.95 (d, 1H, *J*=13.0Hz, one H of pyrimidine -CH_2-), 3.55-3.61 (m, 1H,-C*H*-CH_3), 4.82-4.91 (t, 2H, one H of -CH_2- + 1H of –C*H*-OH), 5.45-5.49 (d, 1H, *J*=16.3 Hz, one H of -CH_2-), 6.82 (bs, 1H, OH, D_2O exchangeable), 7.26-7.29 (q, 2H, py), 7.74-7.79 (m, 1H, py), 8.29 (bs, 1H, NH, D_2O exchangeable), 8.48-8.50 (m, 1H, py); GC-MS: *m/z* 219 (M^+-H_2O, 0.37%); Anal. Calcd. for $C_{11}H_{15}N_3OS$: C, 55.69; H, 6.32; N, 17.72; S, 13.50. Found: C, 55.27; H, 6.17; N, 17.48; S, 13.46%.

4-Hydroxy-3-(4-methoxy-2-nitrophenyl)-6-methyl-tetrahydropyrimidine-2(1*H*)-thione 17

Solvent of elution: EtOAc: MeOH (9:1, v/v); yield 39%; m.p. 140°C; IR (KBr): 3477, 3300 (OH, NH), 1632 (C=N), 1545, 1495 and 1450 (Ar) cm^{-1}.^1H NMR (400 MHz, DMSO-d_6): δ 1.21-1.25 (d, 3H, -CH_3), 1.69-1.76 (m, 1H, one H of pyrimidine -CH_2-), 1.97-2.00 (d, 1H, *J*=12.7 Hz one H of pyrimidine -CH_2-),

3.68-3.73 (m, 1H,-CH-CH_3), 3.87 (s, 3H, -OCH_3), 4.88-4.90 (t, 1H,-CH-OH), 6.57-6.58 (d, 1H, OH, D_2O exchangeable), 7.30-7.38 (m, 2H, Ar), 7.51-7.52 (d, 1H, *J*=2.7 Hz, Ar), 8.70 (bs, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 298 (M^+ + 1, 15%), *m/z* 297 (M^+, 0.7%); Anal. Calcd. for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.05; N, 14.14; S, 10.77. Found: C, 48.34; H, 5.00; N, 13.98; S, 10.48%.

N-(4-Ethoxy-2-(4,4,6-trimethyl-2-thioxo-3,4-dihydropyrimidin -1(2*H*)- yl)phenylacetamide 6

N-(2-amino-4-ethoxyphenyl)acetamide (0.388 g; 2 mmole) was dissolved in acetic acid (5 mL) and to it was added 4-isothiocyanato-4-methyl pentan-2-one (0.31 mL 2 mmole). The reaction contents were allowed to stand at RT for two days. Solvent was distilled and the semi solid residue left behind was basified with 10% aqueous sodium carbonate solution (10 mL). The residue so obtained was filtered off, washed with water to give crude product 6 which was crystallized from methanol to give pure product 6. yield 0.270 g, 40%; m.p. 170°C; IR (KBr): 3357, 3190 (NH), 1688(-$NHCOCH_3$), 1520, 1473 and 1422 (Ar) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.33-1.42 (m, 9H, 2 × -CH_3 + -CH_3), 1.49 (s, 3H, -CH_3), 2.15 (s, 3H, -$COCH_3$), 3.99-4.03 (q, 2H) -OCH2, 4.86 (s, 1H, =CH),6.71-6.72 (d, 1H, *J*=3.0 Hz Ar), 6.88-6.90 (q, 1H, Ar), 7.36-7.38 (d, 1H, *J*=8.0 Hz, Ar), 8.77 (bs, 1H, -N*H*-CO-, D_2O exchangeable), 8.87 (bs, 1H, NH, D_2O exchangeable); ES-MS: *m/z* 356 (MNa^+, 100%), 334 (MH^+, 7%); Anal. Calcd. for $C_{17}H_{23}N_3O_2$ S: C, 61.26; H, 6.90; N, 12.61; S, 9.60. Found: C, 61.19; H, 6.70; N, 12.35; S, 9.27%.

4-Hydroxy-4-methyl-3-(pyridin-2-ylamino)- tetrahydropyrimidine-2(1*H*)-thione 19

2-Hydrazinopyridine (0.218 g; 2 mmole) was taken in methanol (10 mL) and to it was added 4-isothiocyanatobutan-2-one (0.26 mL; 2 mmole). The reaction-mixture was kept at RT for two days. The solvent was allowed to evaporate at RT, the residue (in 5 mL methanol) was adsorbed on silica gel and subjected to column chromatography. Elution with EtOH:MeOH (5:5, v/v) gave pure product 19. yield 0.220 g, 46%; m.p. 130°C; IR (KBr): 3415, 3285 (OH, NH), 1651 (C=N), 1533, 1465 and 1417 (Ar) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.23-1.24 (d, 3H, -CH_3), 1.49-1.51 (d, 1H, *J*=8.5, Hz one H of -CH_2-), 1.71 (d, 1H, one H of -CH_2-), 2.07-2.10 (d, 1H, *J*=15.0 Hz, one H of pyrimidine -CH_2-), 2.29-2.32 (d, 1H, *J*=14.5 Hz one H of pyrimidine -CH_2-), 4.94 (bs, 1H, OH, D_2O exchangeable), 7.04-7.13 (m, 2H, Ar), 8.07-8.16 (m, 2H, Ar), 9.35 (bs, 1H, NH, D_2O exchangeable), 10.1-10.5 (bs, 1H, NH, D_2O exchangeable); GC-MS: *m/z* 187 ($C_{10}H_{11}N_4^+$, 1.02 %); 186 ($C_{10}H_{10}N_4^+$, 1.33%); Anal. Calcd. for $C_{10}H_{14}N_4OS$: C, 50.42; H, 5.88; N, 23.52; S, 13.44. Found: C, 50.34; H, 5.55; N, 23.20; S, 13.08%.

Anti-inflammatory activity

Paw oedema inhibition test was used on albino rats of Charles Foster strain by adopting the method of Winter[25]. Groups of five animals of both sexes (body weight 120-160 g), pregnant females excluded were given a dose of a test compound. Thirty minutes later, 0.20 mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw and the volume was measured by a water plethysmometer apparatus and then measured again 1-3 hr later. The mean increase of paw volume at each time interval was compared with that of control group (five rats treated with carrageenan, but not with test compounds) at the same time intervals and percent inhibition values were calculated by the formula given below.

$$[\%\ \text{anti-inflammatory activity} = [1\text{-}D_t / D_c] \times 100]$$

D_t and D_c are paw volumes of oedema in tested and control groups respectively.

Analgesic activity[26]

Analgesia was measured by the writhing assay using Swiss mice (15-20 g). Female mice were screened for writhing on day one, by injecting intraperitonially 0.2 cm^3 of aqueous solution of phenylquinone. They were kept on a flat surface and the numbers of writhes of each mouse was recorded for 20 min. The mice showing significant writhes (>10) were sorted out and used for analgesic assay on the following day. The mice consisting of 5 in each group and showing significant writhing were given orally a 50 or 100 mg/kg p.o. dose of the test compounds 15 min prior to phenylquinone challenge. Writhing was again recorded for each mouse in a group and a percentage protection was calculated by using the following formula:

Protection = 100-[{(No. writhes in treated mice)/(No. of writhes in untreated mice)} × 100]

This was taken as percent analgesic response and was averaged in each group of mice. Percent of animals exhibiting analgesia was determined with each dose.

Acknowledgement

Two of the authors, (MD and RR) are thankful to UGC and CSIR respectively, New Delhi for financial assistance. We are thankful to technical staff of the Chemistry Department, IIT Roorkee, Roorkee, for the spectroscopic and elemental analysis.

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