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

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A number of pyrimidine derivatives 1-3, 5-19 have been synthesized by condensation of bis(2-(vinloxy))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-methoxy-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-(vinloxy))ethylamine 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 bisvinloxy 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\(\text{H}\) ~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 \(\delta\): 1.88-1.98 (m, 2H, -CH\(_2\)- of pyrimidine) and 5.81-5.83 (d, 1H, OH, D\(_2\)O exchangeable) in the \(^1\)H NMR of 2 and presence of a signal at \(\delta\): 4.77 (s, 1H, =CH-) in the \(^1\)H NMR of 2. These observations confirm elimination of H\(_2\)O from 1 leading to the formation of 2.

Direct condensation of 1a with 1b using methanol as solvent, adjusting p\(\text{H}\) ~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
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 pH ~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-
(aminomethyl) thiophene 4c, 2-thiophene ethylamine 4d, 2-hydrazino pyridine 4e and 1-amino naphthaleine-2-ol hydrochloride 4f with 1b by heating under reflux in methanol after adjusting the pH 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 1c 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(1H) thione by heating compound 18 in methanol under reflux for eight hr at pH ~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 pH ~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 pH ~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 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 (Table I) exhibited 50%, 50%, 50%, 25%, 50%, 25%, 25%, 75%, 25%, 25%, 50%, 50%, 50%, 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.

**Experimental Section**

Melting points were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 FT spectrometer. 1H 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-(vinlyoxy)ethyl)tetrahydro pyrimidine-2(1H)-thione 1

Bis(2-(vinlyoxy)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 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, 1356, 1447 (Ar) cm⁻¹. A white solid was obtained, which was recrystallised with MeOH; yield 75%; m.p. 162°C; IR (KBr): 3227, 3415 (OH, NH), 1537 and 1473 (Ar) cm⁻¹.

14.28; S, 16.32. Found: C, 61.01; H, 7.99; N, 13.98; S, 14.00%. GC-MS: m/z 196 (M⁺, 16%), 182 (M⁺ - CH₂), 135 (M⁺ - CH₃), 127 (M⁺ - CONH₂), 113 (M⁺ - CONH₂ + CH₂), 79 (M⁺ - CONH₂ + CH₂ + CH₃), 55 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄), 43 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅), 31 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅ + CH₆), 19 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅ + CH₆ + CH₇).

Similarly compounds 5 and 18 were also synthesized.

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

Crystallised with MeOH; yield 84%; m.p. 155°C; IR (KBr): 3174 (NH), 1590, 1523 and 1454 (Ar) cm⁻¹. A white solid was obtained, which was recrystallised with MeOH; yield 75%; m.p. 150°C; IR (KBr): 3227, 3415 (OH, NH), 1537 and 1473 (Ar) cm⁻¹.

14.28; S, 16.32. Found: C, 61.01; H, 7.99; N, 13.98; S, 14.00%. GC-MS: m/z 196 (M⁺, 16%), 182 (M⁺ - CH₂), 135 (M⁺ - CH₃), 127 (M⁺ - CONH₂), 113 (M⁺ - CONH₂ + CH₂), 79 (M⁺ - CONH₂ + CH₂ + CH₃), 55 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄), 43 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅), 31 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅ + CH₆), 19 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅ + CH₆ + CH₇).

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

4-Hydroxy-4',6,6-trimethyl-3-(pyridin-2-yl)methyl)tetrahydro pyrimidine-2(1H) thione 18

Crystallised with MeOH; yield 75%; m.p. 160°C; IR (KBr): 3227, 3415 (OH, NH), 1537 and 1473 (Ar) cm⁻¹. A white solid was obtained, which was recrystallised with MeOH; yield 75%; m.p. 150°C; IR (KBr): 3227, 3415 (OH, NH), 1537 and 1473 (Ar) cm⁻¹. A white solid was obtained, which was recrystallised with MeOH; yield 75%; m.p. 150°C; IR (KBr): 3227, 3415 (OH, NH), 1537 and 1473 (Ar) cm⁻¹.

14.28; S, 16.32. Found: C, 61.01; H, 7.99; N, 13.98; S, 14.00%. GC-MS: m/z 196 (M⁺, 16%), 182 (M⁺ - CH₂), 135 (M⁺ - CH₃), 127 (M⁺ - CONH₂), 113 (M⁺ - CONH₂ + CH₂), 79 (M⁺ - CONH₂ + CH₂ + CH₃), 55 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄), 43 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅), 31 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅ + CH₆), 19 (M⁺ - CONH₂ + CH₂ + CH₃ + CH₄ + CH₅ + CH₆ + CH₇).

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

General procedure for pH adjusted reactions

i) First Procedure

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

Bis(2-(vinlyoxy)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 pH of reaction contents was adjusted to ~4 by adding a few drops of 10% H₂SO₄ 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, vacuum dried to give crude product which was crystallized from methanol to give pure product 2. Yield 0.330 g, 73%; m.p. 150°C; IR (KBr): 3174 (NH), 1590, 1523 and 1454 (Ar) cm⁻¹. A white solid was obtained, which was recrystallised with MeOH; yield 75%; m.p. 150°C; IR (KBr): 3227, 3415 (OH, NH), 1537 and 1473 (Ar) cm⁻¹.
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(1H)-thione 7

Crystallized with MeOH; yield 89%; m.p. 160°C; IR (KBr): 3462, 3219 (NH), 1687 (C=O), 1526, 1450 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 1.16 (s, 6H, 2 × -CH₃), 1.90 (s, 3H, =CH-), 4.82 (s, 1H, =CH₂), 5.60 (s, 2H, –CH₂), 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, D₂O exchangeable). GC-MS: no M⁺ peak but other fragmented peaks were observed i.e., m/z 155 (C₅H₃N₂S⁺, 0.08%), 97 (C₄H₃S⁺, 100%), 83 (C₃H₃S⁺, 1.65%). Anal. Calcd. for C₁₅H₁₁N₄S₂: 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(1H)-thione 8

Crystallized with MeOH; yield 52%; m.p. 95°C; IR (KBr): 3470 (NH), 1640 (C=O), 1519, 1443, 1419 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 1.15 (s, 6H, 2 × -CH₃), 1.87 (s, 3H, -CH₃), 3.13 (t, 2H, -CH₂), 4.77 (s, 1H, =CH-), 6.92-6.96 (m, 2H, Ar), 7.35 (dd, 1H, Ar), 8.63 (bs, 1H, NH, D₂O exchangeable); GC-MS: m/z 266 (M⁺, 13.06%); Anal. Calcd. for C₁₂H₁₀N₂S₂: C, 57.14; H, 6.34; N, 11.11; S, 25.39. Found: C, 57.02; H, 6.23; N, 10.98; S, 25.10%.

4-Hydroxy-6-trimethyl-3-(2-(vinyloxy)ethyl)-tetrahydropyrimidine-2(1H)-thione 9
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 CHCl₃: EtOAc (1:9, v/v). IR (KBr): 3234 and 3100 (NH, OH), 1536 and 1447 (Ar) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 0.64–0.76 (m, 4H, –CH₂), 1.12–1.13 (d, 3H, -CH₃), 1.37–1.42 (m, 1H, CH=CH-), 3.51–3.53 (m, 1H, -C=CH-O-), 8.15–4.12 (m, 1H, -CH-OH), 6.19–6.22 (m, 1H, =CH₂), 8.15 (bs, 1H, NH, D₂O exchangeable); GC-MS: m/z 216 (M⁺, 25.34%); Anal. Calcd. for C₁₃H₁₉NO₂S: C, 50.00; H, 7.46; 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(1H)-thione 11
Solvent of elution: CHCl₃: 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-d₆): δ 0.64–0.76 (m, 4H, =CH₂-CH₂-), 1.09–1.07 (d, 3H, J=J=2.0 Hz, -CH₃), 1.37–1.42 (m, 1H, one H of pyrimidine -CH₂-), 1.81–1.83 (d, 1H, J=10.0 Hz, one H of pyrimidine -CH₂-), 2.93–2.96 (m, 1H, CH₃=CH-N=), 3.51–3.53 (m, 1H, -CH₂-CH₃), 4.80–4.81 (t, 1H, -CH-OH), 6.05–6.06 (d, 1H, OH, D₂O exchangeable), 8.15 (bs, 1H, NH, D₂O exchangeable); GC-MS: m/z 168 (M⁺-H₂O, 54.62%);
4-Hydroxy-6-methyl-3-(thiophen-2-ylmethyl)-tetrahydropyrimidine-2(1H)-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-d₆): δ 1.13-1.14 (d, 3H, -CH₃), 1.18-1.19 (m, 1H, one H of pyrimidine -CH₂), 2.13-2.15 (m, 1H, one H of pyrimidine -CH₂), 3.41-3.46 (m, 2H, -CH-CH₃ + OH, D₂O exchangeable), 4.52-4.55 (s + d, 2H, -CH-CH₃ + OH, D₂O exchangeable), 5.70-5.73 (d, 1H, J=15.5 Hz, one H of CH₂), 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, D₂O exchangeable); GC-MS: m/z 208 (M⁺-H₂O, 81.43%); Anal. Calcd. for C₁₀H₁₅N₂O₂S: 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%.

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

Solvent of elution: EtOAc: MeOH (9:1, v/v); yield 88%; m.p. 110°C; IR (KBr): 3317, 3233 (OH, NH), 1534, 1494 and 1444 (Ar) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 1.10-1.18 (d, 3H, -CH₃), 1.35-1.38 (dd, 1H, one H of pyrimidine -CH₂), 1.80-1.82 (d, 1H, J=13.0 Hz one H of pyrimidine -CH₂), 3.16-3.22 (m, 2H, -CH-CH₃ + -CH-OH), 3.43-3.55 (m, 1H, one H of -CH₂), 3.62-3.67 (m, 1H, one H of -CH₂), 4.20-4.30 (m, 1H, one H of -CH₂), 4.73-4.74 (t, 1H, one H of -CH₂), 6.34-6.35 (d, 1H, -OH, D₂O 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, D₂O exchangeable); GC-MS: m/z 224 (M⁺-H₂O, 45.47%); Anal. Calcd. for C₁₀H₁₅N₂O₂S: 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-(2-ethylthiophen-2-yl)methyl)-tetrahydropyrimidine-2(1H)-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-d₆): δ 1.13-1.15 (d, 3H, -CH₃), 1.18-1.19 (m, 1H, one H of pyrimidine -CH₂), 2.13-2.15 (m, 1H, one H of pyrimidine -CH₂), 3.41-3.46 (m, 2H, -CH-CH₃ + OH, D₂O exchangeable), 4.52-4.55 (s + d, 2H, -CH-OH + one H of -CH₂), 5.70-5.73 (d, 1H, J=15.5 Hz, one H of CH₂), 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, D₂O exchangeable); GC-MS: m/z 208 (M⁺-H₂O, 81.43%); Anal. Calcd. for C₁₀H₁₅N₂O₂S: 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%.
3.68-3.73 (m, 1H, -CH=CH-), 3.87 (s, 3H, -OCH3), 4.88-4.90 (t, 1H, -OH), 6.57-6.58 (d, 1H, OH, D2O exchangeable), 7.30-7.38 (m, 2H, Ar), 7.51-7.52 (d, 1H, J=2.7 Hz, Ar), 8.70 (bs, 1H, NH, D2O exchangeable); GC-MS: m/z 298 (M+ 1, 15%), m/z 297 (M+, 0.7%); Anal. Calcd. for C12H13N2O5S: 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(2H)-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 filtered, washed with water to give pure product 6 which was basified with 10% aqueous sodium carbonate solution (10 mL). The residue so obtained was filtered off, washed with water to give pure product 6 which was crystallized from methanol to give pure product 6. Yield 0.220 g, 46%; m.p. 130°C; IR (KBr): 3415, 3285 (OH, NH), 1735 (C=O), 1688 (-NHCOCH3), 1537, 1465 and 1417 (Ar) cm-1. 1H NMR (500 MHz, DMSO-d6): δ 1.33-1.42 (m, 9H, 2 × -CH3 + -CH2-), 1.49 (s, 3H, -CH3), 2.15 (s, 3H, -COCH3), 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, -NH-CO-, D2O exchangeable), 8.87 (bs, 1H, NH, D2O exchangeable); ES-MS: m/z 296 (MNa+, 100%), 334 (MH+, 7%); Anal. Calcd. for C17H19N2O5S: 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(1H)-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. 1H NMR (500 MHz, DMSO-d6): δ 1.23-1.24 (d, 3H, -CH3), 1.49-1.51 (d, 1H, J=8.5, Hz one H of -CH2-), 1.71 (d, 1H, one H of -CH2-), 2.07-2.10 (d, 1H, J=15.0 Hz, one H of pyrimidine -CH2-), 2.29-2.32 (d, 1H, J=14.5 Hz one H of pyrimidine -CH2-), 4.94 (bs, 1H, OH, D2O exchangeable), 7.04-7.13 (m, 2H, Ar), 8.07-8.16 (m, 2H, Ar), 9.35 (bs, 1H, NH, D2O exchangeable), 10.1-10.5 (bs, 1H, NH, D2O exchangeable); GC-MS: m/z 187 (C10H11N4O+, 1.02%); 186 (C10H10N4, 1.33%); Anal. Calcd. for C10H14N4OS: 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 Winter25. 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:

\[
\% \text{ anti-inflammatory activity} = \left[ 1 - \frac{D_1}{D_2} \right] \times 100
\]

D1 and D2 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 cm3 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 plethysmometer apparatus and then measured again 1-3 hr later. The mean increase of writhing 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:

\[
\text{Protection} = 100 - \left\{ \frac{\text{No. writhes in treated mice}}{\text{No. writhes in untreated mice}} \right\} \times 100
\]
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.

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References