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Bioorganic & Medicinal Chemistry 15 (2007) 3334–3344
Bioorganic & Medicinal Chemistry

One pot synthesis of pyrimidine and bispyrimidine derivatives and their evaluation for anti-inflammatory and analgesic activities

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Received 23 January 2007; revised 7 March 2007; accepted 8 March 2007
Available online 13 March 2007

Abstract—A number of pyrimidine derivatives (**1**–**10**) have been synthesized by condensation of 4-isothiocyanato-4-methylpentan-2-one with furfurylamine, histamine, 1-(3-aminopropyl)imidazole, 1-(3-aminopropyl)-2-pyrrolidinone, 2-aminobenzonitrile and 3-isothiocyanatobutanal with 1-(3-aminopropyl)-2-pyrrolidinone and 2-hydrazinopyridine under different reaction conditions. Various bispyrimidine derivatives (**11**–**15**) were obtained by condensation of 4-isothiocyanato-4-methylpentan-2-one with 2,4,8,10-tetraoxaspiro[5,5]undecane3,9-dipropamine (**11′**), 1,4-bis(3-aminopropyl)piperazine (**13′**), 3,5-diamino 1,2,4-triazole (**15′**) and 3-isothiocyanatobutanal with 2,4,8,10-tetraoxaspiro[5,5]undecane 3,9-dipropamine, 1,4-bis(3-aminopropyl)piperazine. All these compounds were characterized by correct FT-IR, ^{1}H NMR, MS and elemental analysis. These compounds were screened for anti-inflammatory and analgesic activities. Anti-inflammatory activity of **3** is comparable while analgesic activity was found to be better than that of standard drug.

1. Introduction

Pain is associated with any kind of health problem and for the management of pain, there is an urgent need of safer anti-inflammatory drugs. Pyrimidine derivatives possessing anti-inflammatory and analgesic activities have been reported in the literature.[1–7] In addition to above-mentioned activities, pyrimidine derivatives possessing antitumour,[8] antimicrobial,[9] antibacterial,[10] antifungal[11] and antiinfective[12] activities have also been reported in the literature. In continuation of our efforts[13–23] in search of potential anti-inflammatory and analgesic molecules we have synthesized a number of pyrimidine and bispyrimidine derivatives and evaluated them for biological activities which we wish to report in this paper.

2. Results and discussion

2.1. Chemistry

Furfurylamine (**1a**; Scheme 1) and 4-isothiocyanato-4-methylpentane-2-one[24] (**1b**) were dissolved in methanol. The reaction contents were allowed to stand at room temperature for 2 days and then solvent was removed at room temperature. To the semisolid residue left behind were added little diethyl ether and ethyl acetate and the reaction contents were scratched. Solid product separated out was filtered and washed thoroughly with cold ethyl acetate to give pure condensed product 3-(furan-2-yl methyl)-4-hydroxy-4,6,6-trimethyl tetrahydropyrimidine-2(1*H*) thione (**1**; Scheme 1). ^{1}H NMR (500 MHz; $CDCl_3$) of **1** shows signals at δ 1.24 (s, 3H, CH_3); 1.39 (s, 3H, CH_3); 1.67 (s, 3H, CH_3); 2.02–2.05 (d, 1H, $J = 15$ Hz, one H of pyrimidine CH_2); 2.10–2.13 (d, 1H, $J = 15$ Hz, one H of pyrimidine CH_2); 2.96 (br s, 1H, OH, exch); 4.85–4.88 (d, 1H, $J = 15$ Hz, one H of CH_2); 5.84–5.87 (d, 1H, $J = 15$ Hz, one H of CH_2); 6.34 (dd, 1H, $J = 2$ and 3.5 Hz, Ar); 6.53 (dd, 1H, $J = 1$ and 3.5 Hz, Ar); 6.57 (br s, 1H, NH exch); 7.35 (dd, 1H, $J = 1$ and 2 Hz, Ar). GC–MS did not show M^+ ion peak but gave M^+–H_2O peak at *m*/*z* 236 (40.48%). This can be due to *tert*-OH being very labile and undergoing elimination very fast. FT-IR spectra show absorption bands at 3423 and 3233 (–OH, –NH–), and 1534 (Ar) cm^{-1}. Spectral data of compound **1** fully support the structure assigned to it. Formation of **1** can be explained by nucleophilic attack of –NH_2 of **1a** on isothiocyanato group of **1b** giving a non-isolable intermediate thiourea **1′** (Scheme 1) and further nucleophilic attack by –NH– to >C═O group giving a ring cyclized hydrated product **1** (Scheme 1).

Keywords: Ketoisothiocynate; Pyrimidine; Bispyrimidine; Anti-inflammatory; Analgesic.
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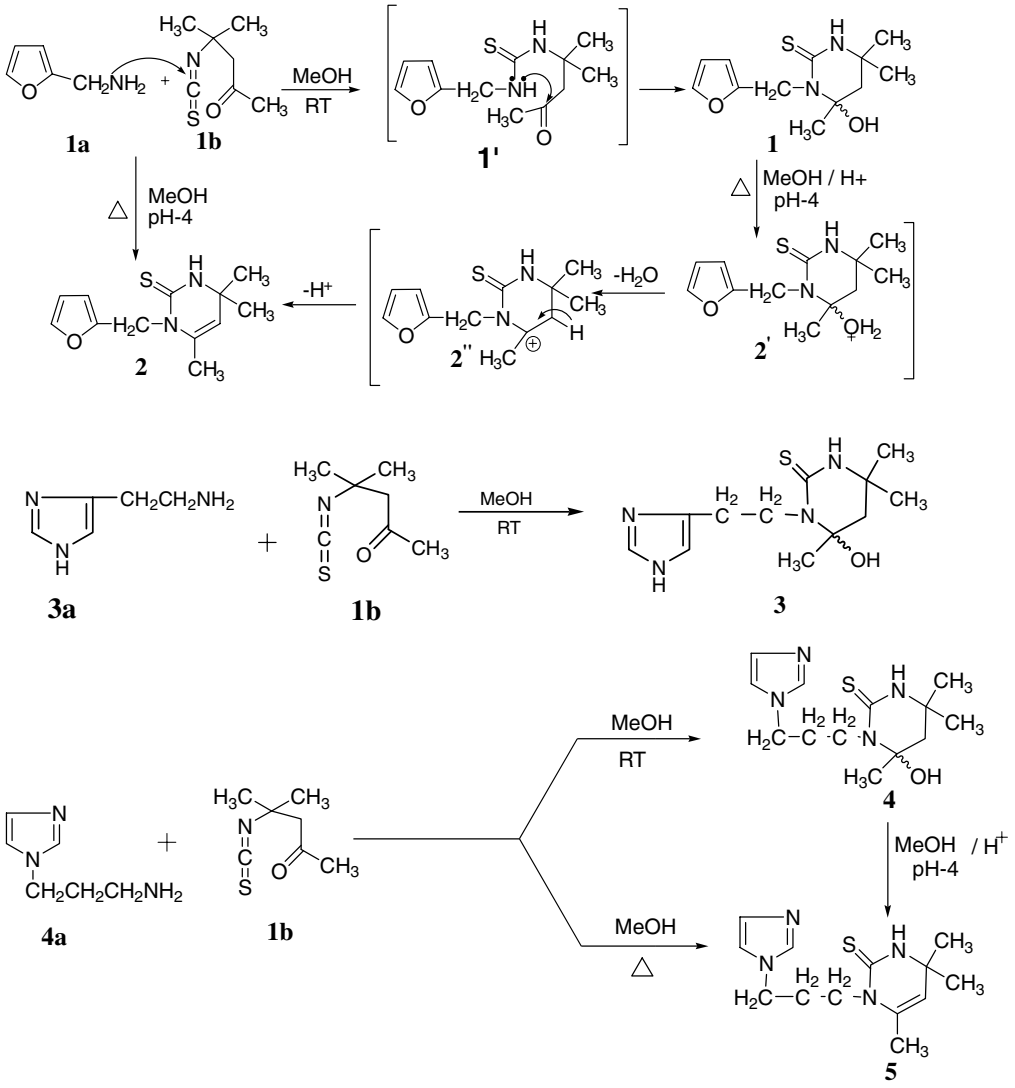
doi:10.1016/j.bmc.2007.03.028

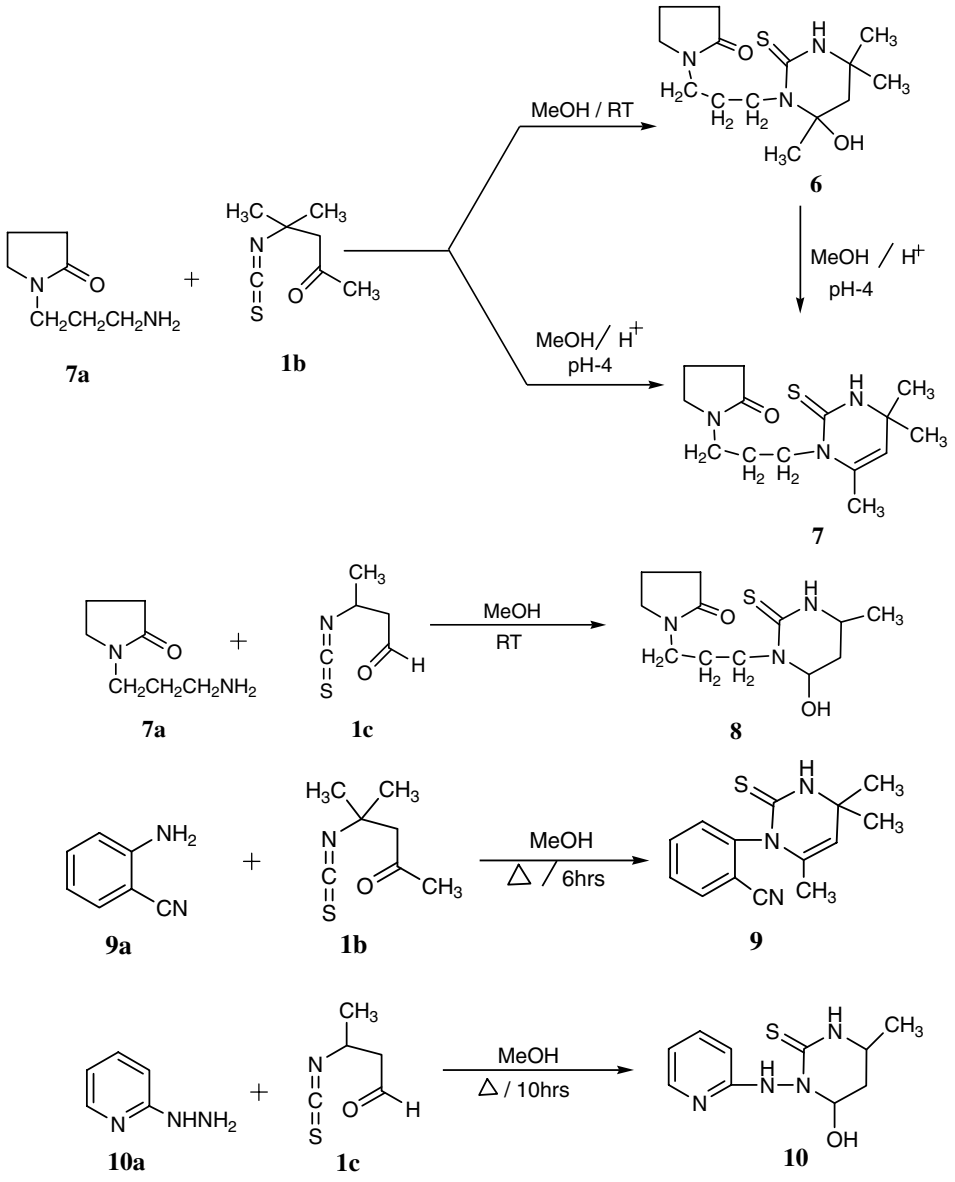


Scheme 1.

When compound **1** was heated in methanol under reflux for 8 h at pH ~4, dehydrated product, that is, 1-(furan-2-yl methyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)thione (**2**; Scheme 1) was obtained in good yield. ^{1}H NMR (500 MHz; DMSO-d_6) of **2** shows signals δ 1.02 (s, 6H, 2× CH_3); 1.92 (s, 3H, CH_3); 4.72 (s, 1H, =CH–); 5.30 (s, 2H, –CH_2–); 6.12–6.13 (d, 1H, Ar); 6.27–6.30 (q, 1H, Ar); 7.44–7.47 (d, 1H, Ar); 8.63 (s, 1H, NH, exch). GC–MS gave M^+ ion peak at *m*/*z* 236 (30.34%). FT-IR spectra show absorption bands at 3221 (–NH–) and 1521 (Ar) cm^{-1}. Spectral data of **2** are in complete agreement with the structure assigned to it. Dehydration will occur through non-isolable intermediates **2**′ and **2**″ (Scheme 1).

A comparison of ^{1}H NMR of **1** and **2** indicates absence of signals at δ 2.02–2.05 (d, 1H one H of –CH_2– of pyrimidine ring), 2.10–2.13 (d, 1H, one H of CH_2 of pyrimidine) and 2.96 (br s, 1H, OH, exch) in the ^{1}H NMR of **2** and presence of a signal at δ 4.72 (s, 1H, =CH–). These observations confirm elimination of H_2O from **1** leading to the formation of **2**. In case of compound **2** C_6-carbon of pyrimidine ring is attached to a double bond and is sp^2 hybridized and thus does not affect –CH_2– attached to furan ring and hence shows a singlet in ^{1}H NMR, whereas in case of compound **1** C_6-carbon of pyrimidine ring is sp^3 hybridized and is attached to one methyl and one hydroxyl group due to the effect of C_6–OH group which is in close vicinity of –CH_2– of furan ring both the protons becoming different and giving geminal coupling and hence appearing as two doublets. Direct condensation of **1a** with **1b** using methanol as solvent and adjusting pH to ~4 and heating under reflux, on usual work up, gave compound **2** (Scheme 1). The yield of product **2** obtained by direct condensation was slightly less than what was obtained by dehydration of **1** and **2**.

Condensation of histamine (**3a**) with 4-isothiocyanato-4-methylpentan-2-one (**1b**) in methanol at room temperature gave 6-hydroxy-1[2-(1*H* imidazo-4-yl)-ethyl]-4,4,6-trimethyl tetrahydropyrimidine-2-thione (**3**; Scheme 1). The structure of compound **3** is fully supported by spectral data reported in the Section 4 of this paper. Condensation of 1-(3-aminopropyl) imidazole **4a** with **1b** at room temperature using methanol as solvent gave



Scheme 1. (*continued*)

1-(3-(1*H*-imidazol-1-yl) propyl)-6-hydroxy-4,4,6-trimethyl tetrahydro pyrimidine-2(1H)-thione (**4**; Scheme 1). Spectral data of **4** reported in the experimental section of this paper are in agreement with the structure assigned to it. Compound **4** when heated under reflux in methanol after adjusting pH of the reaction mixture to ~4 undergoes dehydration to give product 1-(3-(1*H*-imidazol-1-yl)propyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*) thione (**5**; Scheme 1).The structure of compound **5** is fully supported by spectral data reported in experimental section of this paper. EI-MS of **5** gave M^+ ion peak at *m*/*z* 264 (M^+, 53%). Interestingly, compound **5** gave all the fragmentation peaks which are also shown by compound **4** after loss of H_2O molecule, that is, *m*/*z* 264 ($M^+ - H_2O$; 58.3). Fragmentation pattern of compound **4** is explained in Figure 1. Compound **5** was also obtained by direct condensation of **4a** and **1b** by refluxing in methanol for eight hours and then purifying the product by column chromatography. The yield obtained for **5** by conversion of **4** to **5** was much better than the product **5** obtained by direct condensation of **4a** and **1b**. Condensation of 1-(3-aminopropyl)-2-pyrrolidinone **7a** and 4-isothiocyanato-4-methylpentan-2-one (**1b**) at room temperature using methanol as solvent of reaction gave condensed product **6**, that is, 1-(3-(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydropyrimidine-1(2*H*)-yl) propyl) pyrrolidin-2-one. When compound **6** was heated under reflux using methanol as solvent and adjusting the pH of reaction mixture to ~4 (by adding a few drops of 10% sulfuric acid in methanol) compound **6** undergoes dehydration to give 1,3-(4,4,6-trimethyl-2-thioxo-3,4-dihydropyrimidine-1(2*H*)-propyl)pyrrolidin-2-one (**7**) in good yield. The structures assigned to compounds **6** and **7** are in full agreement with their spectral data reported in experimental section of this paper. Direct condensation of **7a** and **1b** by refluxing in methanol and adjusting the pH to ~4 gave lower yield of **7** than obtained from conversion of **6** to **7**.

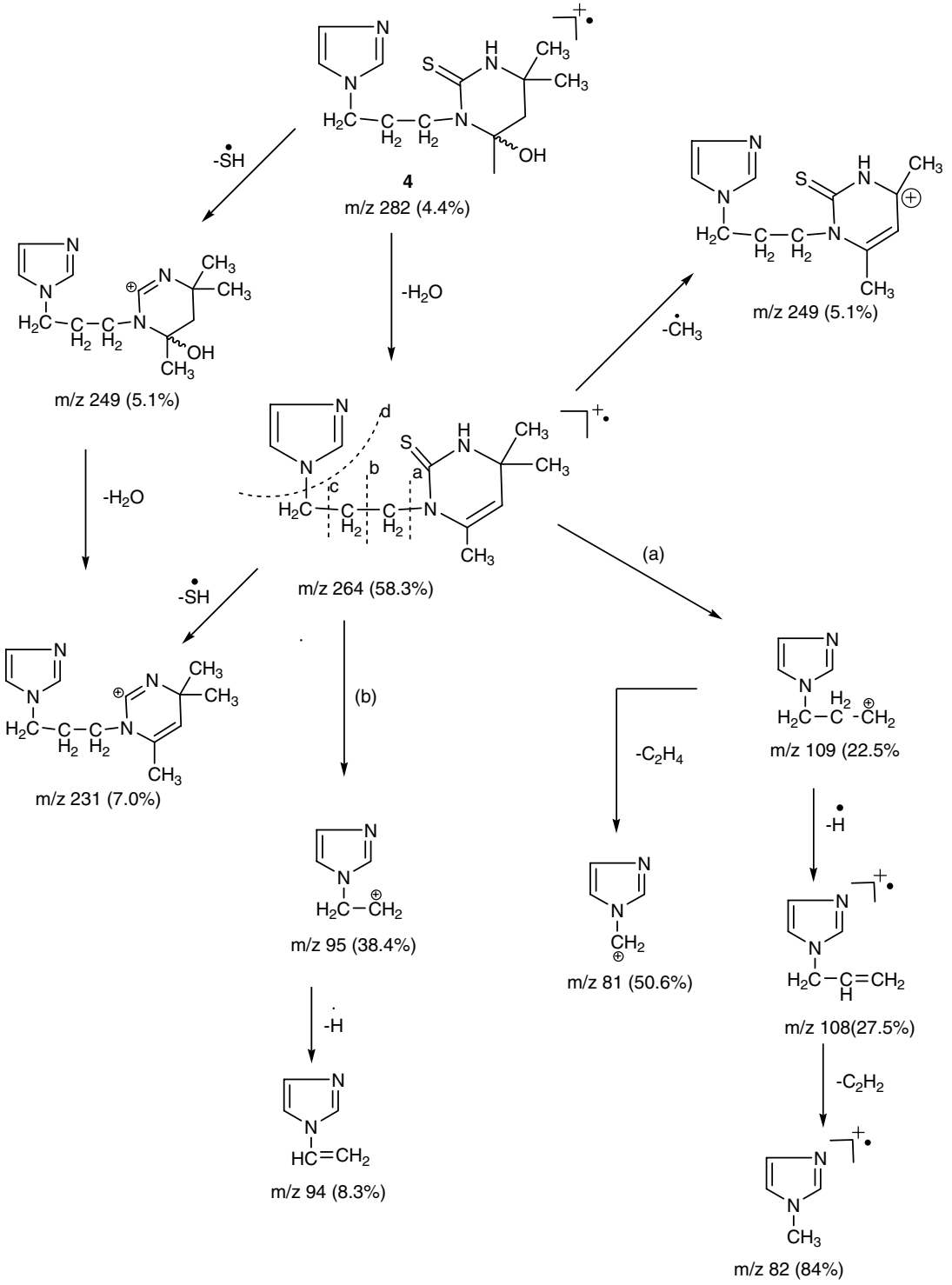


Figure 1.

Pyrrolidinone **7a** on condensation with 3-isothiocyanatobutanal[25] (**1c**; Scheme 1) at room temperature gave product **8**, that is, 1-(3-(6-hydroxy-4-methyl-2-thioxo-tetrahydropyrimidine-1(2*H*)-yl)-propyl)pyrrolidin-2-one. Spectral data of **8** reported in experimental section of this paper fully support the structure assigned to it. 2-Aminobenzonitrile (**9a**; Scheme 1) on condensation with 4-isothiocyanato-4-methylpentan-2-one (**1b**; Scheme 1) by refluxing for 6 h, using methanol as solvent, gave condensation product 2-(4,4,6-trimethyl-2-thioxo-3,4-dihydropyrimidin-1(2*H*)-yl)benzo-nitrile (**9**; Scheme 1) in good yield. Condensation of 2-hydrazinopyridine - (**10a**) with 3-isothiocyanatobutanal (**1c**; Scheme 1) by refluxing in methanol for 10 h and then purifying the crude product by column chromatography over silica gel (elution $CHCl_3$ EtOA, 1:1) gave 4-hydroxy-6-methyl-3(pyridin-2-ylamino)-tetrahydropyrimidine-2(1*H*)thione (**10**; Scheme 1). Spectral data of **9** and **10** reported in Section 4 of this

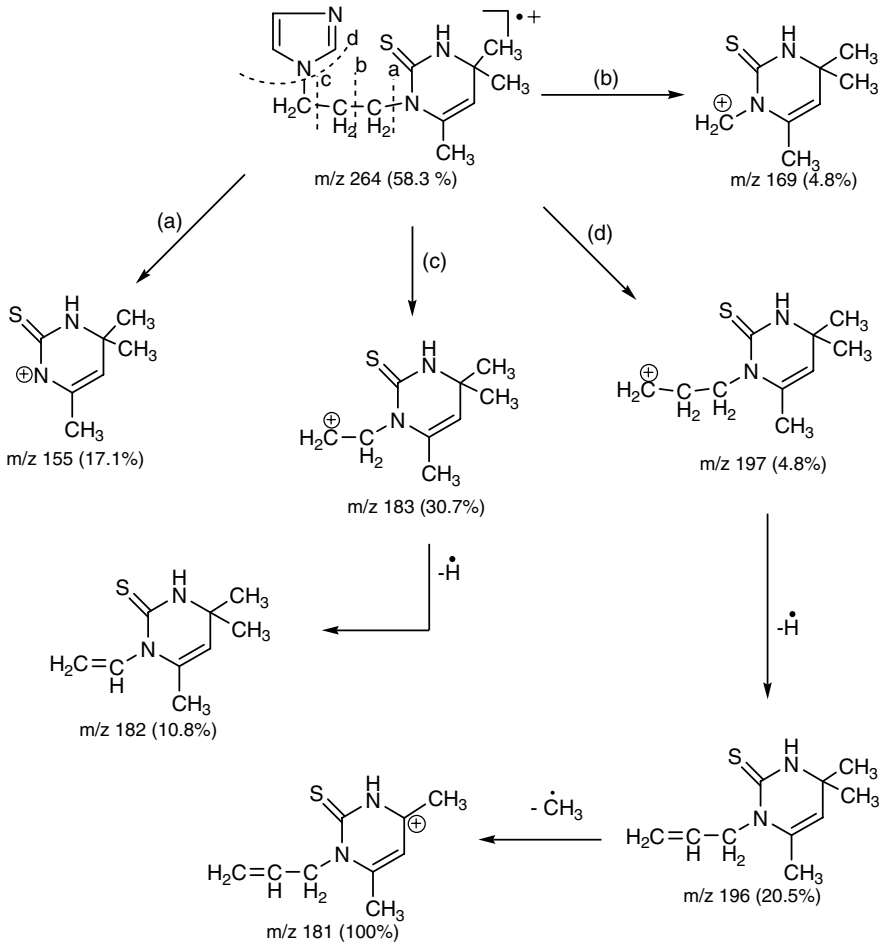
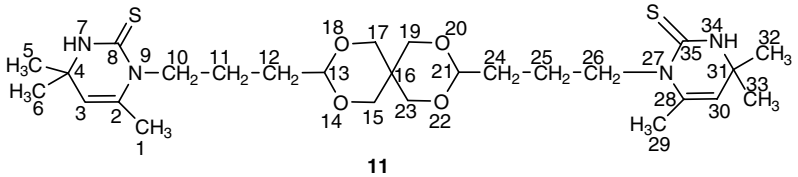


Figure 1. (*continued*)

paper fully support the structures assigned to them. 2,4,8,10-Tetraoxaspiro[5,5]undecane 3,9-dipropamine (**11′**; Scheme 2) on condensation with 4-isothiocyanato-4-methylpentan-2-one (**1b**; Scheme 2) at room temperature using methanol as a solvent gave condensed product 1-(3-(9-(3-((4,6,6,-trimethyldihydro pyrimidine-2(1*H*)thione)-4-ene-3yl)propyl)2,4,8,10-tetraoxaspiro[5,5]undecan-3-yl)propyl)-4,4,6-trimethyldihydro pyrimidine-2(1*H*)thione (**11**; Scheme 1) in 50% yield. While interpreting ^{1}H NMR of **11** peak positions were assigned with the help of ^{1}H NMR of starting material, that is (**11′**). It is considered that dioxane ring starting with C_{13} is in the plane and dioxane ring starting with C_{21} is out of plane.

^{1}H NMR (200 MHz; DMSO-d_6) δ 1.20–1.22 (2s, looking like a doublet, 12H, 4× CH_3 i.e., $C_5C_6C_{32}C_{33}$); 1.63–1.65 (m, 4H, 2× CH_2; $C_{11}C_{25}$); 1.71–1.76 (m, 4H, 2× CH_2; $C_{12}C_{24}$); 1.93 (s, 6H, 2× CH_3; C_1C_{29}), 3.33–3.37 (t, 2H, C_{19a} and C_{23a}), 3.52–3.58 (t, 4H, 2× CH_2; $C_{10}C_{26}$); 4.09–4.27 (m, 4H, 2× CH_2; C_{17},C_{15}); 4.49–4.57 (q, 4H, C_{13},C_{21},C_{19b} and C_{23b}); 4.73 (s, 2H, 2×=CH–); 7.52 (s, 2H, 2× NH, exch). IR (KBr) υ_{max} 3178 (NH) cm^{-1}. FAB-MS of **11** gave MH^+ ion peak at *m/z* 553 (50%). The structure of **11** is fully supported by IR, ^{1}H NMR, elemental analysis and FAB-MS spectral data. During condensation of 3-isothiocyanatobutanal (**1c**; Scheme 2) with **11′** at room temperature using methanol as a solvent pure condensed product, that is, 1-(3-(9-(3-((4-hydroxo-6-methyl tetrahydro pyrimidin-2(1*H*)thione)3yl)propyl)-2,4,8,10-tetraoxaspiro[5,5]undecan-3-yl)propyl)-6-hydroxo-4-methyltetrahydropyrimidine-2(1*H*)thione (**12**; Scheme 2), was obtained only after chromatographic separation of the crude product. Yield of the pure condensed product **12** was 36%. Structure assigned to **12** is in complete agreement with its spectral data reported in Section 4 of this paper.

When 1,4-bis(3-aminopropyl) piperazine (**13′**; Scheme 2) and 4-isothiocyanato-4-methylpentan-2-one (**1b**; Scheme 2) dissolved in methanol were kept at room temperature



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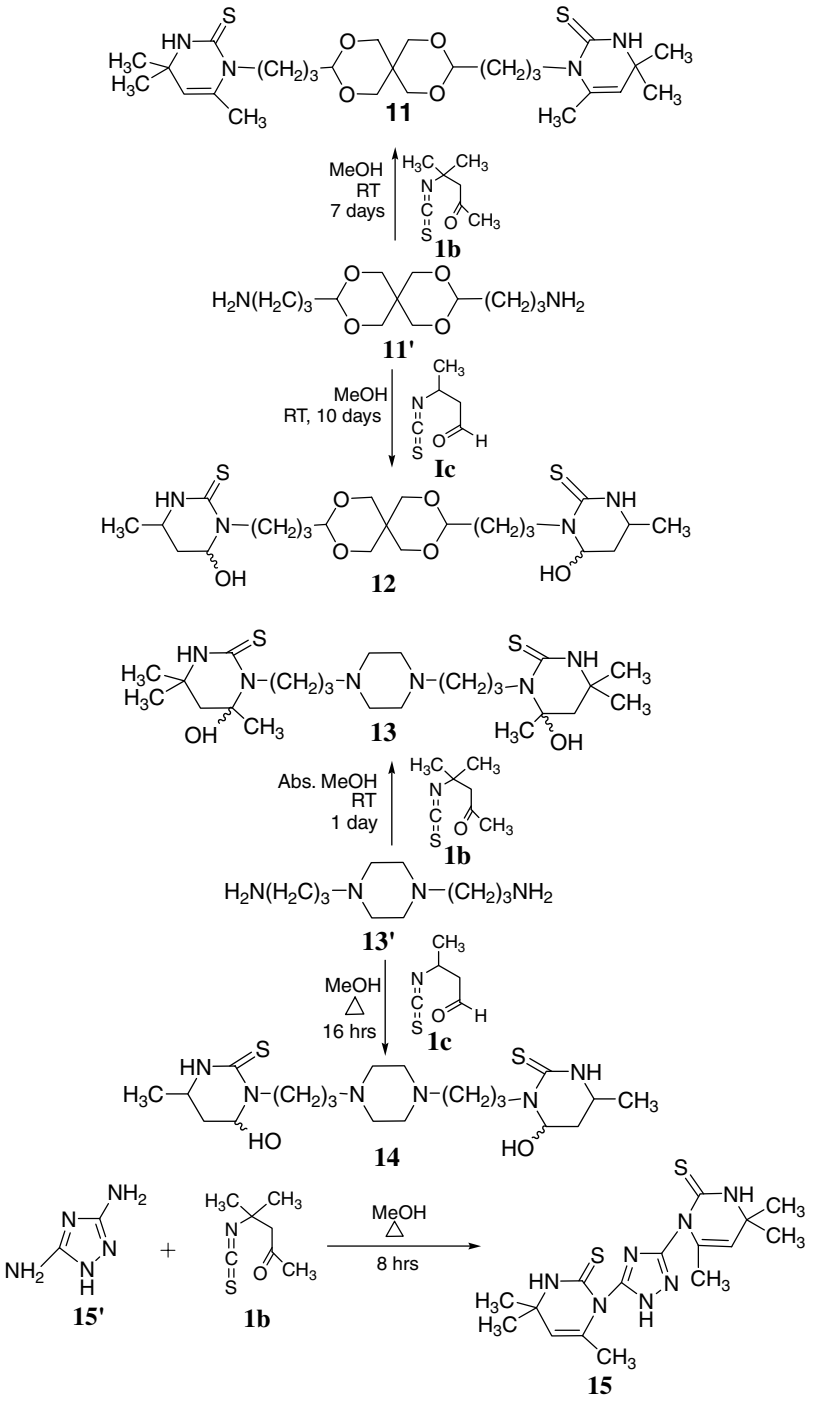

Scheme 2.

for one day, solid product separated out which on filtration and washing with chilled methanol gave pure product **13** in 50% yield. Structure assigned to **13**, that is, 4-hydroxy-3-(3-(4-(3-(6-hydroxy-4,4,6-trimethyl-2-thioxotetrahydropyrimidin1(2*H*)yl)propyl) piperazin-1-yl)propyl)-4,4,6-trimethyl tertahydropyrimidin-2-(1*H*)-thione, is completely supported by spectral data reported in Section 4 of this paper. Condensation of 1,4-bis(3-aminopropyl)piperazine (**13′**; Scheme 2) with 3-isothiocyanatobutanal (**1c**; Scheme 2) at room temperature using methanol as a solvent gave complex mixture which was difficult to separate and hence the same reaction was carried out by refluxing the reaction mixture for 16 h. Removal of solvent and recrystallization of the crude product from ethyl acetate methanol (1:1) gave condensed product 4-hydroxy-3-(3-(4-(3-(6-hydroxy-4-methyl-2-thioxo-tetrahydropyrimidin-1(2*H*)-yl)propyl)piperazin-1-yl)propyl)-6-methyl-tetrahydropyrimidine-2(1*H*)-thione (**14**; Scheme 2) in 50% yield. Spectral data of **14** reported in experimental section of this paper are in complete agreement with the structure assigned to it. 3,5-Diamino-1,2,4-triazole (**15′**) on reaction with 4-isothiocyanato-4-methylpentan-2-one (**1b**) at room temperature gave complex mixture but the same reaction on heating under reflux in methanol gave crude product which

was purified by column chromatography over silica gel. Elution with ethyl acetate chloroform (1:1) gave condensation product 4,4,6-trimethyl-1-(5-(4,4,6-trimethyl-2-thioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2H-1,2,4-triazol-3-yl)-3,4-dihydropyrimidine-2(1*H*)thione (**15**; Scheme 2) in 30% yield. Low yield of the product could be due to the ring nitrogen of triazole making both the amino groups less reactive. Structure of **15** is derived from its correct spectral data reported in Section 4 of this paper.

2.2. Biological results

Anti-inflammatory activity[26] evaluation of **1**–**6**, **8**, **9**, **11**–**15** was carried out using carrageenin-induced paw oedema assay and results are summarized in Table 1. Compounds **3**, **4**, **6**, **9**, **11**, **12**, **15** at 100 mg/kg po; and compounds **1**, **2**, **5**, **8**, **13**, **14** at 50 mg/kg po exhibited 65%, 35%, 40.3%, 0.0%, 31.8%, 0.0%, 0.0% and 10.3%, 15.1%, 32.5%, 36.3%, 31.6%, 38.6% activity, respectively, whereas ibuprofen exhibited 66.8% anti-inflammatory activity at 100 mg/kg po. Analgesic activity[27] evaluation of **1**–**6**, **8**, **9**, **11**–**15** was carried out using phenyl quinone writhing assay and results are summarized in Table 1. Compounds **3**, **4**, **6**, **9**, **11**, **12**, **15** at 100 mg/kg po; and compounds **1**–**5**, **8**, **9**, **11**, **13**, **14** at 50 mg/kg po exhibited 100%, 50%, 34%, 25%, 75%, 0.0%, 0.0% and 15%, 8.5%, 25%, 25%, 40%, 50%, 0.0%, 25%, 10.0%, 40.0% analgesic activity, respectively, whereas ibuprofen exhibited 75% and 50% analgesic activity at 100 mg and 50 mg/kg po, respectively. A look at Table 1 indicates that compounds **3**, **4**, **6**, **8**, **14** exhibited good anti-inflammatory activity, whereas compounds **3** and **8** exhibited good analgesic activity.

3. Conclusion

A number of pyrimidine (**1**–**10**) and bispyrimidine (**11**–**15**) derivatives have been synthesized and screened for anti-inflammatory and analgesic activities. Compounds **3** and **8** exhibited good anti-inflammatory and analgesic activities, whereas **4**, **6** and **14** exhibited good anti-inflammatory activity. Compound **3** exhibited anti-inflammatory activity comparable to ibuprofen and analgesic activity better than ibuprofen.

4. Experimental

Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 FT spectrometer. ^{1}H NMR spectra were measured on a Bruker WH-500, 300 and 200 spectrometer at a ca. 5–15% (w/v) solution in DMSO-d_6 or $CDCl_3$ (TMS as internal standard). FAB-MS was recorded on JEOL SX-120 (FAB) spectrometer. GC–MS was recorded on Perkin-Elmer Clarus 500 mass spectrometer. Elemental analysis was carried out on Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (254 nm). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60–120 mesh).

4.1. General procedure for room temperature reactions

4.1.1. Synthesis of 3-(furan-2-yl methyl)-4-hydroxy-4,6,6-trimethyltetrahydro pyrimidine-2(1*H*)-thione (1). Furfuryl amine (0.20 ml; 2 mmol) was taken in methanol (10 ml) and to it was added 4-isothiocyanato-4-methylpentan-2-one (0.30 ml; 2 mmol). The reaction contents were allowed to stand at room temperature for two days. Solvent was allowed to evaporate at room temperature and the semisolid residue left behind was scratched with chilled ethyl acetate diethyl ether (1:1) (5 ml). The solid separated out was filtered and washed with chilled ethyl acetate to give pure condensed product **1**. Yield 0.290 g (57%), mp 95 °C IR and ^{1}H NMR data has already been reported in Section 2. GC–MS (*m*/*z*; relt

Table 1. Anti-inflammatory and analgesic activity evaluation of compounds **1**–**6**, **8**, **9**, **11**–**15**

Compound	Dose mg/kg po	Anti-inflammatory activity %	Dose mg/kg po	Analgesic activity %
1	50	10.3	50	15
2	50	15.1	50	8.5
3	100	65	100	100
			75	50
			50	25
			25	12.5
4	100	35	100	50
			50	25
5	50	32.5	50	40
6	100	40.3	100	34
8	50	36.3	50	50
9	100	0.0	100	25
			50	0.0
11	100	31.8	100	75
			50	25
12	100	0.0	100	0.0
13	50	31.6	50	10.0
14	50	38.6	50	40.0
15	100	0.0	100	0.0
Ibuprofen	100	66.8	100	75
			50	50

int %) 236 (40.48%), 221 (6.06%), 155 (5.72%), 96 (3.23%), 81 (100%).

Anal. Calcd for $C_{12}H_{18}N_2O_2S$ C, 56.96; H, 7.08; N, 11.02; S, 12.59; found C, 56.81; H, 7.32; N, 11.00; S, 12.91.

Similarly, 6-hydroxy-1[2-(1*H* imidazol-4-yl)-ethyl]-4,4,6-trimethyl-tetrahydro pyrimidine-2-thione (**3**, at room temperature for 3 days; product separated out, washed with chilled methanol), 1-(3-(1*H*-imidazol-1-yl)propyl)-6-hydroxy-4,4,6-trimethyl tetrahydropyrimidine-2(1*H*)thione (**4**; at room temperature, for one day; product separated out, washed with chilled methanol), 1-(3-(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydropyrimidine-1(2*H*)-yl)propyl)pyrrolidin-2-one (**6**; at room temperature, for 1 day; product separated out, washed with chilled methanol), and 1-(3-(6-hydroxy-4-methyl-2-thioxo-tetrahydropyrimidin-1(2*H*)-yl)propyl)pyrrolidin-2-one (**8**; at room temperature for 3 days, remove solvent at room temperature, residue left behind was scratched with ethyl acetate ethanol (9:1) and solid separated out was washed with chilled methanol) were synthesized.

4.1.2. Synthesis of 6-hydroxy-1-[2-(1*H*-imidazol-4-yl)ethyl]-4,4,6-trimethyl-tetrahydropyrimidine-2-thione (3). Solvent of crystallization: methanol, yield 55% mp 180 °C, IR (KBr) υ_{max} 3395 and 3191(–OH, NH), 1533 (Ar). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (s, 3H, CH_3); 1.37 (s, 3H, $–CH_3$); 1.81 (br s, 1H, –OH, exch); 1.86 (s, 3H, CH_3); 2.45 (d, 1H, J = 14.5 Hz, 1H of pyrimidine CH_2); 2.55 (d, 1H, J = 14.5 Hz, 1H of pyrimidine CH_2) 2.82–3.14 (m, 2H, CH_2); 3.47–3.62 (m, 1H, one H of CH_2); 5.64–5.74 (m, 1H, one H of CH_2); 6.80 (s, 1H, Ar); 6.87 (s, 1H, NH, exch); 7.48 (s, 1H, Ar). FAB-MS *m*/*z* 251 ($MH^+ - H_2O$; 25%). Anal. Calcd for $C_{12}H_{20}N_4OS$ C, 53.73; H, 7.46; N, 20.89; S, 11.94; found C, 53.99; H, 7.05; N, 21.03; S, 12.01.

4.1.3. Synthesis of 1-(3-(1*H*-imidazol-1-yl)propyl)-6-hydroxy-4,4,6-trimethyl-tetrahydropyrimidine-2(1*H*)-thione (4). Solvent of crystallization: methanol, yield 70%, mp 170 °C, IR (KBr) υ_{max} 3250 and 3177 (OH, NH) 1525 (Ar). ^{1}H NMR[28] (400 MHz, DMSO-d_6) δ 1.14 (s, 3H, CH_3); 1.23 (s, 3H, CH_3); 1.37 (s, 3H, $–CH_3$); 1.88 (d, 1H, J = 14 Hz, 1H of pyrimidine CH_2); 1.94 (d, 1H, J = 14 Hz, 1H of pyrimidine CH_2); 2.02 (m, 1H, one H of CH_2); 2.34 (m, 1H, one H of CH_2); 3.65–3.67 (m, 2H, $–CH_2–$); 3.96–3.99 (m, 2H, $–CH_2–$); 5.91 (s, 1H, OH, exch); 6.89 (s, 1H, Ar); 7.17 (s, 1H, Ar); 7.63 (s, 1H, Ar); 8.13 (s, 1H, NH, exch). EI-MS (*m*/*z*; relt int %) 282 (M^+, 4.4%); 264 (58.3%); 249 (5.1%); 231 (7.0); 197 (4.8%); 196 (20.5%); 183 (30.7%); 182 (10.8%); 181 (100%); 169 (4.8%); 155 (17.1%); 109 (22.5%); 108 (27.5%); 95 (38.4%); 94 (8.3%); 82 (84%); 81 (50.6%). Anal. Calcd for $C_{13}H_{22}N_4OS$ C, 55.31; H, 7.80; N, 19.85; S, 11.34; found C, 55.63; H, 7.40; N, 19.51; S, 11.29.

4.1.4. Synthesis of 1-3-(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydropyrimidine-1(2*H*)-ylpropyl)-pyrrolidin-2-one (6). Solvent of crystallization: methanol, yield 70% mp 175 °C, IR (KBr) υ_{max} 3324 and 3204 (–OH, NH), 1655 (>C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.10 (s, 3H, CH_3); 1.20 (s, 3H, CH_3); 1.40 (s, 3H, CH_3); 1.75–1.80 (m, 1H, one H of CH_2); 1.90–2.00 (m, 4H, 2× CH_2); 2.00–2.10 (m, 1H, one H of CH_2); 2.12–2.15 (t, 2H, $–CH_2–$); 3.19 (m, 2H, CH_2); 3.45 (m, 2H, CH_2); 3.68 (m, 2H, CH_2); 5.90 (s, 1H, –OH, exch); 8.03 (s, 1H, NH, exch). TOF MS ES *m*/*z* 282.0582 ($MH^+ - H_2O$, 100%). Anal. Calcd for $C_{14}H_{25}N_3O_2S$ C, 56.18; H, 8.36; N, 14.09; S, 10.70; found C, 55.91; H, 7.87; N, 13.59; S, 10.39.

4.1.5. Synthesis of 1-3-(6-hydroxy-4-methyl-2-thioxo-tetrahydropyrimidine-1(2*H*)-ylpropyl)-pyrrolidin-2-one (8). Solvent of crystallization: THF, Yield 50%, mp 175 °C, IR (KBr) υ_{max} 3452 and 3273 (–OH, NH), 1652 (>C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.20–1.22 (d, 3H, CH_3); 1.51–1.55 (m, 1H, one H of CH_2); 1.85–2.20 (m, 5H, 4H, 2× CH_2) + (1H one H of $–CH_2–$); 2.32–2.38 (t, 2H, $–CH_2–$); 3.40–3.49 (m, 4H, 2×CH_2); 3.62–3.71 (m, 2H, CH_2); 3.90–3.97 (m, 1H,); 4.86–4.87 (t, 1H,); 6.41–6.42 (d, 1H, OH, exch); 7.36 (s, 1H, NH, exch). FAB-MS *m*/*z* 272 (MH^+, 40%); 254 ($MH^+ - H_2O$, 100%). Anal. Calcd for $C_{12}H_{21}N_3O_2S$ C, 53.13; H, 7.74; N, 15.49; S, 11.80; found C, 52.82; H, 7.72; N, 15.75; S, 11.78.

4.2. General procedure for pH adjusted reactions

4.2.1. Synthesis of 1-(furan-2-yl methyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione (2). Compound **1** (254 mg; 1 mmol) was dissolved in methanol (10 ml) and pH of the reaction mixture was adjusted to ~4 by adding a few drops of 10% H_2SO_4 in methanol. The reaction contents were heated under reflux for eight hours, solvent was removed under reduced pressure and the residue left behind was treated with 10% sodium bicarbonate solution. The solid product so separated was filtered, washed with water and recrystallized from chloroform to give pure product **2**. Yield 0.165 g (70%). Mp 115 °C IR and ^{1}H NMR data have already been reported in Section 2. GC–MS *m*/*z* 236 (M^+, 30.34%), 221 (4.51%), 155 (4.62%), 81 (100%). Anal. Calcd for $C_{12}H_{16}N_2OS$ C, 61.01; H, 6.77; N, 11.86; S, 13.56; found C, 60.87; H, 7.10; N, 12.13; S, 13.37.

Similarly, 1-(3-(1H-imidazol-1-yl)propyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione (**5**) and 1-(3-(4,4,6-trimethyl-2-thioxo-3,4-dihydropyrimidine-1(2H)-yl)propyl)pyrrolidin-2-one (**7**) were synthesized.

4.2.2. Synthesis of 1-(3-(1*H*-imidazol-1-yl)propyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione (5). Solvent of recrystallization: $CHCl_3$ EA (1:1). Yield 25%; mp 120 °C, IR (KBr) υ_{max} 3203 (NH) 1637 (C=N) 1526 (Ar). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (s, 3H, CH_3); 1.12 (s, 3H, CH_3); 1.77 (s, 3H, CH_3); 1.99 (m, 2H, $–CH_2–$); 4.00–4.14 (m, 4H, 2× CH_2); 4.78 (s, 1H, =CH–); 6.87 (s, 1H, Ar); 7.19 (s, 1H, Ar); 7.64 (s, 1H, Ar); 8.55 (s, 1H, NH, exch). EI-MS *m*/*z* 264 (M^+, 53%). Anal. Calcd for $C_{13}H_{20}N_4S$ C, 59.09; H, 7.57; N, 21.21; S, 12.12; found C, 59.38; H, 7.41; N, 21.65; S, 12.01.

4.2.3. Synthesis of 1-3-(4,4,6-trimethyl-2-thioxo-3,4-dihydropyrimidine-1(2*H*)-propyl)pyrrolidin-2-one (7). Solvent of recrystallization: methanol. Yield 69%, mp 120 °C, IR (KBr) υ_{max} 3449 (–NH), 1678 (>C=O). ^{1}H NMR

(500 MHz; DMSO-d_6) δ 1.12 (s, 9H, 3× CH_3); 1.73 (m, 2H, CH_2); 1.88 (m, 4H, 2× CH_2); 2.34 (m, 2H, CH_2); 2.97 (m, 2H, CH_2); 3.96 (m, 2H, CH_2); 4.79 (s, 1H, =CH–); 8.50 (s, 1H, NH, exch). GC–MS *m/z* 281 (M^+, 9.23%); 266 (8.51%); 248 (38.19%); 197 (1.27%); 196 (4.07%); 183 (4.89%); 155 (21.82%); 126 (100.0%); 98 (40.57%). Anal. Calcd for $C_{14}H_{23}N_3OS$ C, 59.78; H, 8.18; N, 14.93; S, 11.39; found C, 60.01; H, 8.48; N, 14.59; S, 11.73.

4.3. Second procedure

4.3.1. Synthesis of 1-(furan-2-yl methyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione (2). Furfurylamine (0.20 ml; 2 mmol) was taken in methanol (10 ml) and to it was added 4-isothiocyanato-4-methyl pentan-2-one (0.30 ml; 2 mmol). The pH of reaction contents was adjusted to ~4 by adding few drops of 10% H_2SO_4 in methanol. The reaction mixture was heated under reflux for 6 h and then solvent was removed under reduced pressure. The residue left behind was treated with 10% sodium bicarbonate solution and the solid obtained was filtered, washed with water and recrystallized from methanol to give pure product **2**. Yield 0.329 g (70%). mp 115 °C, IR (KBr) υ_{max} 3221 (NH), 1521 (Ar). ^{1}H NMR (500 MHz; DMSO-d_6) δ 1.02 (s, 6H, 2× CH_3); 1.92 (s, 3H, CH_3); 4.73 (s, 1H, =CH–); 5.30 (s, 2H, –CH_2–); 6.12–6.13 (d, 1H, Ar); 6.27–6.30 (q, 1H, Ar); 7.44–7.47 (d, 1H, Ar); 8.63 (s, 1H, NH, exch). GC–MS *m/z* 236 (M^+, 30.34%), 221 (4.51%), 155 (4.62%), 81 (100%). Similarly, compound **7** was synthesized (yield 60%; recrystallization MeOH). Compounds **2** and **7** obtained by route (i) and (ii) were found to be same.

4.3.2. Synthesis of 1-(3-(1*H*-imidazol-1-yl)propyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1*H*)-thione (5). 1-(3-Aminopropyl)imidazole (0.25 ml; 2 mmol) was taken in absolute methanol (10 ml) and to it was added 4-isothiocyanato-4-methylpentan-2-one (0.32 ml; 2 mmol). The reaction mixture was heated under reflux for 8 h and then the solvent was removed under reduced pressure. The semisolid residue left behind was subjected to column chromatography over silica gel. Elution with ethyl acetate chloroform (1:1) gave condensed product **5**. Yield 0.132 g (25%). Mp 120 °C, IR (KBr) υ_{max} 3203 (NH) 1637 (C=N) 1526 (Ar). ^{1}H NMR (400 MHz; DMSO-d_6) δ 1.08 (s, 3H, CH_3); 1.12 (s, 3H, CH_3); 1.77 (s, 3H, CH_3); 1.99 (m, 2H, –CH_2–); 4.00–4.14 (m, 4H, 2× CH_2); 4.78 (s, 1H, =CH–); 6.87 (s, 1H, Ar); 7.19 (s, 1H, Ar); 7.64 (s, 1H, Ar); 8.55 (s, 1H, NH, exch). EI-MS *m/z* 264 (M^+, 53%). All other prominent fragmentation peaks obtained were same as in case of compound **4**. Compound **5** obtained by above method and obtained by dehydration of **4** was found to be same. Anal. Calcd for $C_{13}H_{20}N_4S$ C, 59.09; H, 7.57; N, 21.21; S, 12.12; found C, 59.38; H, 7.41; N, 21.65; S, 12.01.

4.4. Synthesis of 2-(4,4,6-trimethyl-2-thioxo-3,4-dihydropyrimidin-1(2*H*)-yl)benzo-nitrile (9)

4-Isothiocyanato-4-methylpentan-2-one (0.32 ml; 2 mmol) and anthranilonitrile (236 mg; 2 mmol) were taken in 10 ml methanol and the reaction mixture was heated under reflux for 6 h. Solvent was removed under reduced pressure and the crude product so obtained was recrystallized from methanol to give pure product **9**. Yield 0.360 g (70%). Mp 215 °C, IR (KBr) υ_{max} 3181 (NH), 2227 (CN), 1537 (Ar). ^{1}H NMR (200 MHz; DMSO-d_6) δ 1.37–1.53 (3s, 9H, 3× CH_3); 4.92 (s, 1H, =CH–); 7.33 (s, 1H, NH, exch); 7.44–7.52 (m, 2H, Ar); 7.63–7.73 (m, 2H, Ar). FAB-MS *m/z* 258 (MH^+, 100%). Anal. Calcd for $C_{14}H_{15}N_3S$ C, 65.36; H, 5.83; N, 16.15; S, 12.45; found C, 65.02; H, 6.11; N, 16.32; S, 12.19.

4.5. Synthesis of 4-hydroxy-6-methyl-3-(pyridin-2-yl amino)-pyrimidine-2(1*H*)-thione (10)

3-Isothiocyanatobutanal (0.26 ml; 2 mmol) and 2-hydrazinopyridine (0.220 g; 2 mmol) were taken in methanol (20 ml). The reaction contents were heated under reflux for 10 h and then solvent was removed under reduced pressure. The crude product so obtained was purified by column chromatography over silica gel. Elution with $CHCl_3$ removed side products and further elution with ethyl acetate chloroform (1:1) gave pure product **10**. Yield 0.100 g (20%). Mp 120 °C, IR (KBr) υ_{max} 3454 and 3190 (OH, NH), 1531 (Ar) cm^{-1}. ^{1}H NMR (300 MHz; DMSO-d_6) δ 1.27–1.29 (d, 3H, CH_3), 1.96–2.17 (m, 2H, CH_2), 3.76–3.86 (m, 1H, $-\underset{H}{\overset{|}{C}}-CH_3$), 4.87–4.88 (t, 1H,), 6.65–6.68 (d, 1H, Ar), 6.77 (s, 1H, NH, exch), 6.82–6.86 (t, 1H, Ar), 7.52–7.55 (t, 2H, 1H exch NH + 1H Ar), 8.21–8.22 (d, 1H, Ar). FAB-MS. No M^+ ion peak but (MH^+-H_2O) ion peak at *m/z* 221 (50%) was observed. Anal. Calcd for $C_{10}H_{14}N_4SO$ C, 50.42; H, 5.88; N, 23.52; S, 13.44; found C, 50.73; H, 5.66; N, 23.19; S, 13.72.

4.6. Synthesis of 1-(3-(9-(3-((4,6,6,-trimethyldihydropyrimidine-2(1*H*)thione)-4-ene-3yl)propyl)2,4,8,10-tetraoxaspiro[5,5]undecan-3-yl)propyl)-4,4,6-trimethyldihydro pyrimidine-2(1*H*)thione (11)

2,4,8,10-Tetraoxaspiro[5,5]undecane3,9-dipropanamine (274 mg; 1 mmol) was dissolved in methanol (5 ml) and to it was added 4-isothiocyanato-4-methyl-pentan-2-one (0.32 ml; 2 mmol). The reaction contents were allowed to stand at room temperature for 7 days and then filtered to give condensed product which was washed with chilled methanol to give pure product **11**. Yield 0.276 g (50%), mp 190 °C. Spectral data of compound **11** has already been reported in Section 2. Anal. Calcd for $C_{27}H_{44}N_4S_2O_4$ C, 58.69; H, 7.97; N, 10.14; S, 11.60; found C, 58.27; H, 8.01; N, 10.31; S, 11.38.

4.7. Synthesis of 1-(3-(9-(3-((4-hydroxo-6-methyl tetrahydro pyrimidin-2(1*H*)thione)-3yl)propyl)-2,4,8,10-tetraoxaspiro[5,5]undecan-3-yl)propyl)-6-hydroxo-4-methyl-tetrahydropyrimidine-2(1*H*)thione (12)

2,4,8,10-Tetraoxaspiro[5,5]undecane3,9-dipropanamine (274 mg; 1 mmol) and 3-isothiocyanatobutanal (0.26 ml; 2 mmol) were taken in methanol (10 ml). Reaction contents were allowed to stand at room temperature for 10 days. No solid product separated out. Solvent of the reaction mixture was removed under reduced pressure and the residue left behind was purified by column

chromatography over silica gel. Elution with ethyl acetate:methanol (1:1) gave condensed product **12**. Yield 0.192 g (36%); mp 130 °C, IR (KBr) υ_{max} 3444 (OH), ^{1}H NMR (200 MHz, DMSO-d_6 + D_2O) δ 1.25–1.28 (d, 6H, 2× CH_3), 1.56–1.91 (m, 12H, 6× CH_2), 3.32–3.36 (d, 2H), 3.45–3.65 (m, 5H), 3.86–3.91 (t, 3H), 4.02 (m, 1H), 4.51–4.54 (t, 4H, 2× CH_2), 4.90–4.95 (m, 1H), 5.94–5.97 (t, 1H), 6.37–6.47 (t, 1H), FAB-MS *m*/*z* 533 (MH^+, 10%) Anal. Calcd for $C_{23}H_{40}N_4O_6S_2$ C, 51.87; H, 7.51; N, 10.52; S, 12.03; found C, 52.01; H, 7.39; N, 10.68; S, 11.87.

4.8. Synthesis of 4-hydroxo-3-(3-(4-(3-(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydropyrimidin-1(2*H*)-yl)propyl)-piperazin-1-yl)propyl)-4,6,6-trimethyl-tetrahydropyrimidine-2(1*H*)-thione (13)

4-Isothiocyanato-4-methyl pentan-2-one (0.32 ml; 2 mmol) was added to a solution of 1,4-bis(3-aminopropyl) piperazine (0.20 ml; 1 mmol) in absolute methanol (5 ml). The reaction contents were allowed to stand at room temperature for 1 day. Solid product separated out was filtered, washed with methanol to give pure condensed product **13**; Yield 0.267 g (50%); mp 210 °C. IR (KBr) υ_{max} 3400 + 3312 (–OH, NH), ^{1}H NMR (400 MHz; DMSO-d_6) δ 1.15 (s, 6H, 2× CH_3), 1.24 (s, 6H, 2× CH_3), 1.44 (s, 6H, 2× CH_3), 1.68 (m, 2H), 1.91 (q, 4H, 2× CH_2), 2.10 (m, 2H), 2.24–2.35 (m, 10H, 5× CH_2); 3.16–3.17 (q, 2H, CH_2); 3.74–3.76 (t, 4H, 2× CH_2), 6.16 (s, 2H, 2× OH, exch), 8.01 (s, 2H, 2× NH, exch). TOF MS ES *m*/*z* 515.3203 (MH^+, 100%) calculated for $C_{24}H_{47}N_6O_2S_2$ *m*/*z* 515.3202. Anal. Calcd for $C_{24}H_{46}N_6O_2S_2$ C, 56.03; H, 8.94; N, 16.34; S, 12.45; found C, 55.81; H, 8.73; N, 16.51; S, 12.19.

4.9. Synthesis of 4-hydroxo-3-(3-(4-(3-(6-hydroxy-4-methyl-2-thioxo-tetrahydropyrimidin-1(2*H*)-yl)propyl)piperazin-1-yl)propyl)-6-methyl-tetrahydropyrimidine-2(1*H*)-thione (14)

1,4-Bis(3-aminopropyl) piperazine (0.20 ml; 1 mmol) was taken in methanol (10 ml) and to it was added 3-isothiocyanatobutanal (0.26 ml; 2 mmol). The reaction contents were heated under reflux for 16 h and then solvent was removed under reduced pressure. The crude product so obtained was scratched with ethyl acetate:methanol (1:1). Solid product separated out was filtered and washed with cold ethyl acetate. The crude product so obtained was recrystallized from ethyl acetate; Yield 0.230 g (50%). Mp 100 °C; IR (KBr) υ_{max} 3350, 3212 (OH, NH), ^{1}H NMR (200 MHz; DMSO-d_6 + $CDCl_3$) δ 1.23–1.30 (dd, 6H, 2× CH_3), 1.40–2.30 (m, 6H), 2.30–2.90 (m, 16H), 3.25–3.80 (m, 4H), 4.10–4.20 (m, 1H), 4.45–4.55 (m, 1H), 4.90–5.00 (m+s, 2H), 6.80–6.90 (2s, 2H, 2× NH, exch). FAB-MS *m*/*z* 459 (MH^+, 100%). Anal. Calcd for $C_{20}H_{38}N_6O_2S_2$ C, 52.40; H, 8.29; N, 18.34; S, 13.97; found C, 52.11; H, 8.37; N, 18.12; S, 14.03.

4.10. Synthesis of 4,4,6-trimethyl-1-(5-(4,4,6-trimethyl-2-thioxo-3,4 dihydro pyrimidin-1(2*H*)-yl)-2*H*-1,2,4-triazol-3-yl)-3,4-dihydropyrimidine-2(1*H*)thione (15)

3,5-Diamino-1,2,4-triazole (200 mg; 2 mmol) was dissolved in methanol (20 ml) and to it was added 4-isothiocyanato-4-methyl pentan-2-one (0.64 ml; 4 mmol). The reaction contents were heated under reflux for eight hours and then solvent was removed under reduced pressure to give crude product which was purified by column chromatography over silica gel. Elution with $CHCl_3$ removed side products and further elution with chloroform ethyl acetate (1:1) gave pure product **15**. Yield 0.226 g (30%); mp 240 °C, IR (KBr) υ_{max} 3194 (NH) 1546 (Ar). ^{1}H NMR (200 MHz; DMSO-d_6 + $CDCl_3$) δ 1.35 (s, 12H, 4× CH_3), 1.70 (s, 6H, 2× CH_3), 4.79 (s, 2H, 2× =CH–), 8.22 (s, 2H, 2× NH, exch). FAB-MS *m*/*z* 378 (MH^+, 80%). Anal. Calcd for $C_{16}H_{23}N_7S_2$ C, 50.92; H, 6.10; N, 25.99; S, 16.97; found C, 51.07; H, 5.97; N, 25.71; S, 17.13.

4.11. Anti-inflammatory activity evaluation

Anti-inflammatory activity evaluation[26] was carried out using carrageenin-induced paw oedema in albino rats. Oedema in one of the hind paws was induced by injection of carrageenin solution (0.1 ml of 1%) into planter aponeurosis. The volume of the paw was measured plethysmographically immediately after and three hours after the injection of the irritant. The difference in volume gave the amount of oedema developed. Percent inhibition of the oedema between the control group and compound-treated groups was calculated and compared with the group receiving a standard drug. Anti-inflammatory activity of compounds **1**–**6**, **8**, **9**, **11**–**15** screened is reported in Section 2.

4.12. Analgesic activity evaluation

Analgesia was measured by the writhing assay[27] using Swiss mice (15–20 g). Female mice were screened for writhing on day-1 by injecting intraperitoneally 0.2 cm^3 of 0.02% aqueous solution of phenylquinone. They were kept on flat surface and the number 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 five in each group and showing significant writhing were given orally a 25 or 50 or 100 mg/kg po 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 using the following formula:

$$\text{Protection} = 100 - [(\text{No. of writhings for treated mice})/(\text{No. of writhings for untreated mice}) \times 100].$$

This was taken as a percent of analgesic response and was averaged in each group of mice. Percent of animals exhibiting analgesia was determined with each dose. Compounds **1**–**6**, **8**, **9**, and **11**–**15** were screened for analgesic activity and results are reported in Section 2.

Acknowledgments

We are thankful to technical staff of the Chemistry Department, I.I.T, Roorkee, for spectroscopic studies and elemental analysis. Ms Shubhi Jain is thankful to

MHRD, Govt of India, and Ms Monica Dinodia (SRF) to UGC, Delhi, for financial assistance.

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