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Synthesis of condensed pyrimidines and their evaluation for anti-inflammatory and analgesic activities

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Condensation of 4-isothiocyanato-4-methylpentane-2-one with 1,2-diaminocyclohexane, 3-amino-2-naphthol, 1-amino-2-naphthol hydrochloride, 3-amino-2-naphthoic acid, 1,3-diamino-2-hydroxypropane and 1,3-diaminoguanidine hydrochloride give condensation products **1** and **3-8** respectively whereas condensation of 3-isothiocyanato butanal with 1,2-diaminocyclohexane and 1,3-diaminoguanidine hydrochloride give compounds **2** and **9**. All these compounds have been characterized by FT-IR, ^{1}H NMR, MS and elemental analysis. Compounds **1, 2, 4** and **6-9** have been screened for anti-inflammatory and analgesic activity. Compounds **1** and **8** exhibit good analgesic activity whereas all other compounds exhibit moderate anti-inflammatory and analgesic activity.

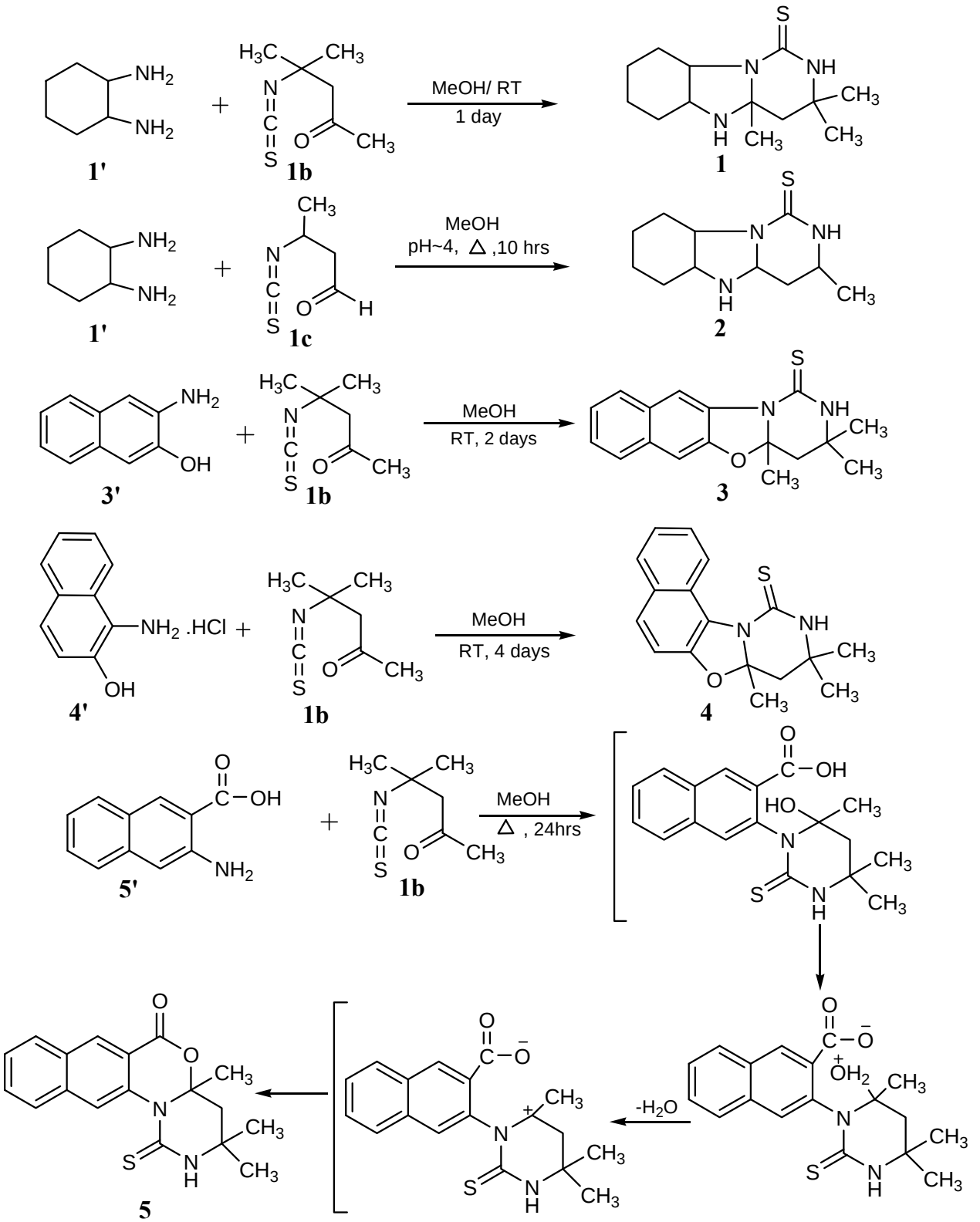
Keywords: Synthesis, condensed pyrimidine, anti-inflammatory, analgesic, screening

Pyrimidine and condensed pyrimidine derivatives possessing anti-inflammatory and analgesic activity is well documented in litrature[1-8]. Apart from anti-inflammatory and analgesic activity these molecules also exhibit a wide variety of other biological activity such as fungicidal[9], antiviral[10-12], anti-HIV[13], anti-hypertensive[14], for treatment of neurological and psychiatric disorder[15] and hyper uricemia[16], *etc*. The wide variety of activity exhibited by condensed pyrimidine derivatives invites the attention of researchers who are involved in the search for new potent molecules. In continuation of the interest[17-26] in the search for potent molecules possessing anti-inflammatory and analgesic activity, a number of condensed pyrimidine derivatives have been synthesized and evaluated for anti-inflammatory and analgesic activity, which is now being reported in this paper.

Results and Discussion

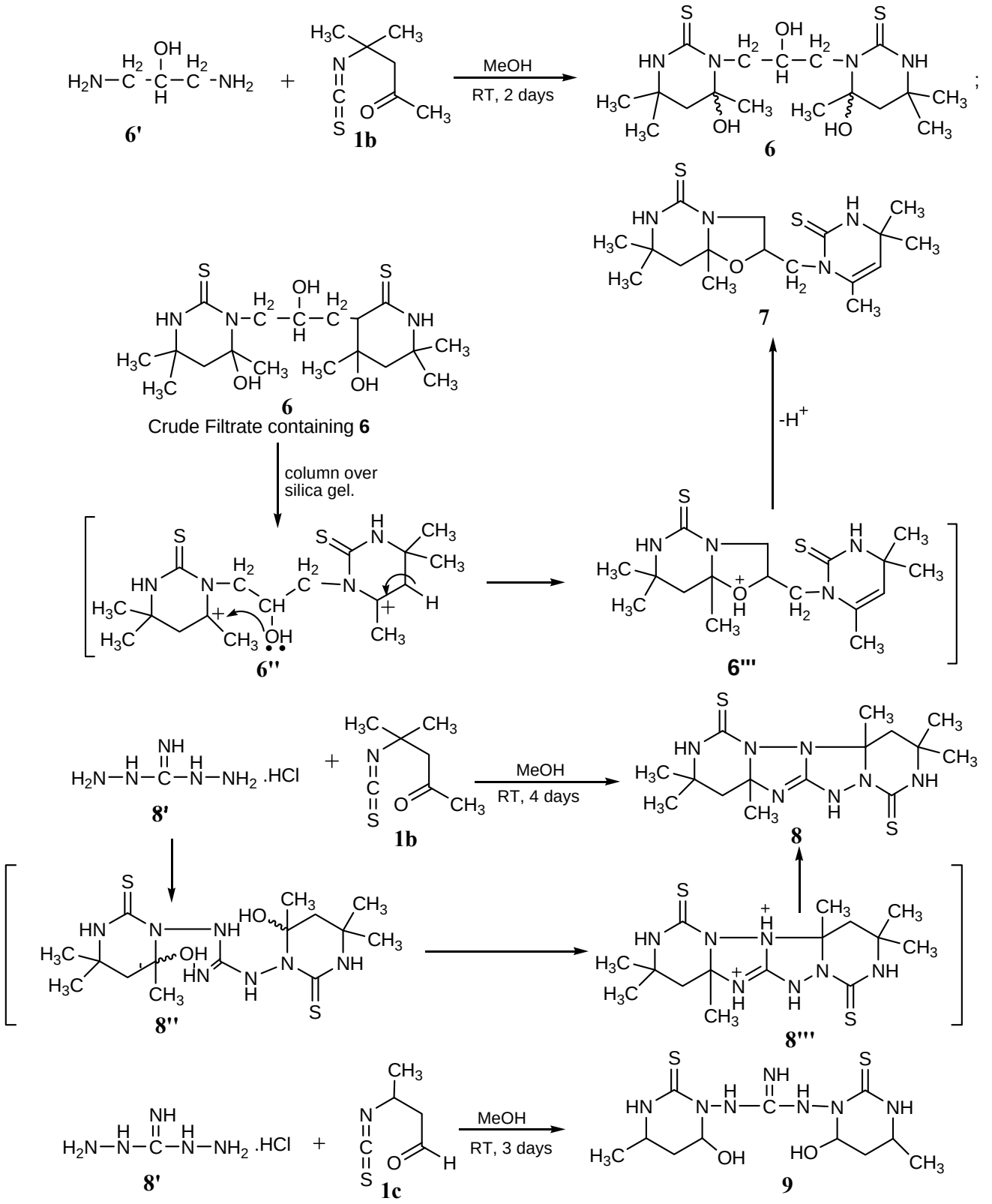
Chemistry

1,2-Diaminocyclohexane (**1′**, **Scheme I**) on condensation with 4-isothiocyanto-4-methylpentan-2-one[27] (**1b**, **Scheme I**) at RT gave the condensation product **1**, *i.e.*, 3,3,4a-trimethyldecahydro-benzo[4,5]-imidazo[1,2-*c*]pyrimidine-1-thione in good yield. ^{1}H NMR (500 MHz DMSO-d_6) of **1** shows signals at δ 1.14-1.38 (m+3s, 13H, 3× CH_3 + 2×CH_2); 1.63-1.66 (d, 1H, one H of pyrimidine-CH_2-); 1.72-1.76 (m, 2H, -CH_2-); 1.90-1.92 (d, 1H,-CH-); 2.15-2.18 (d, 1H, one H of pyrimidine -CH_2-); 2.71-2.74 (d, 1H, -NH- exch); 2.80-2.89(m, 2H,-CH_2-);3.25-3.27 (d, 1H,-CH-); 7.72 (s,1H, -NH- exch). GC-MS: *m/z* 253 (M^+; 38.15%). IR (KBr) shows absorption band at 3212 cm^{-1} (NH). Spectral data of **1** fully supports the structure assigned to it. Condensation of 1,2-diamino-cylohexane with 3-isothiocyanatobutanal[28] (**1c**, **Scheme I**) by refluxing in methanol after adjusting the *p*H of the reaction mixture to about 4 (by adding a few drops of 10% H_2SO_4 in MeOH) gave the condensed product 3-methyl-decahydro-benzo[4,5] imidazo[1,2-*c*]pyrimidine-1-thione **2** (**Scheme I**). Spectral data of compound **2** reported in the experimental section of this paper fully supports the structure assigned to it. 3-Amino-2-naphthol (**3', Scheme I**) was dissolved in methanol by warming and the reaction contents were then allowed to cool to RT. To this cooled solution was added 4-isothiocyanato-4-methyl-pentan-2-one. The reaction mixture was allowed to stand at RT for 4 days and the solvent was then removed under reduced pressure and the crude product so obtained was purified by column chromatography over silica gel. Elution with



Scheme I — *Contd*

—Contd



Scheme I

chloroform removed the side product and further elution with chloroform:ethyl acetate (9:1) gave the pure desired product **3**. Spectral data of 2,2,11a-trimethyl-1, 2, 3, 11a-tetrahydro-11-oxa-3, 4a,-diaza-benzo[*b*]fluorene-4-thione **3** reported in experimental section this paper is in complete agreement with the structure assigned to it. Similarly, condensation of 1-amino-2-naphthol hydrochloride **4'** with 4-isothio-cyanato-4-methylpentan-2-one, after purification by column chromatography (elution by ethyl acetate:methanol 7:3) gave the tetracyclic product **4** in 50% yield. Spectral data of 7a,9,9-trimethyl-7a,8,9,10-tetrahydro-7-oxa-10, 11a-diaza-benzo[*c*]flo-urene-11-thione **4** reported in the experimental section of this paper fully support the structure assigned to it. 3-Amino-2-naphthoic acid **5'** on refluxing with 4-isothiocyanato-4-methylpentan-2-one for 24 hr using methanol as a solvent gave tetracyclic compound **5** (**Scheme I**). The crude product **5** was purified by column chromatography over silica gel (elution, $CHCl_3$:ethyl acetate 1:1). IR (KBr) spectrum of **5** gave absorption band at 3398 (-NH-), 1725 (ester) and 1534 cm^{-1} (Ar). FAB-MS of **5** gave MH^+ ion peak at *m/z* 327 (80%). ^{1}H NMR spectral data of **5** reported in experimental section this paper fully supports the structure assigned to it. The possible mechanism for formation 3,3,4a,-trimethyl-1-thioxo-2,3,4,4a-tetrahy-dro-1*H*-5-oxa-2,12b-diaza-benzo[*a*]-anthracen-6-one **5** is outlined in **Scheme I**. After gaining experience by condensing different compounds having one or two functional groups with 4-isothiocyanato-4-methylpentan-2-one it was considered worthwhile to try condensation of 4-isothiocyanato-4-methylpentan-2-one with multifunctional group containing compounds. Thus, condensation of 1,3-diamino-2-hydroxypropane and 1,3-diaminoguanidine hydro-chloride with isothiocyanato ketones was studied and is being reported here. A solution of 1,3-diamino-2-hydroxy propane and 4-isothiocyanato-4-methyl-pentan-2-one in methanol was allowed to stand at RT for 2 days. The solvent was allowed to evaporate at RT. The semi solid mass left behind was triturated with a mixture of ethyl acetate and diethyl ether (5 mL + 1 mL). Some solid product separated out, which was filtered, washed with chilled methanol and air dried to give the pure product **6**. Spectral data of **6** reported in experimental section of this paper fully supports the structure assigned to it. Since the yield of product **6** was only 25%, it was considered worthwhile to purify the crude mixture left behind by column chromatography over silica gel. The crude mixture was dissolved in methanol and then to it was added silica gel (for column chromatography). The solvent was removed under reduced pressure and the crude product thus adsorbed over silica gel was subjected to column chromatography. Elution with chloroform gave another pure product, which was found to be **7**. The structure assigned to **7** is fully supported by IR, ^{1}H NMR and FABMS spectral data reported in the experimental section of this paper. Formation of **7** can arise from **6** during column chromatography and usual work up. In compound **6** there are two tertiary and one secondary hydroxyl group present. Thus, compound **6** can easily lose two molecules of water (as shown in **Scheme I**) to give dehydrated product **7**. As done in the case of **6',** similarly, 1,3-diaminoguanidine monohydrochloride **8'** was condensed with 4-isothiocyanato-4-methyl-pentan-2-one **1b**, at RT using methanol as solvent. Removal of solvent after 4 days and trituration with ethyl acetate:methanol (1:2) did not give any pure product, so the entire reaction mixture was subjected to column chromatography over silica gel. Elution with ethyl acetate removed side products and further elution with ethyl acetate:methanol (9:1) gave the pure product **8** (**Scheme I**). On the basis of spectral data reported in the experimental section of this paper, the compound **8** was found to be 3,3,4a,7,7,8a-hexamethyl-2, 3, 4, 4a, 7, 8, 8a, 10-octahydro-6*H*-2,4b,4c,6,9,10,10a-heptaaza-indeno[1,2-*a*]indene-1,5-dithione. The probable mechanism for formation of **8** is mentioned in **Scheme I** and product **8** is formed *via* through non-isolable intermediates **8''** and **8'''**. 1,3-Diaminoguanidine monohydrochloride **8'** was condensed with 3- isothiocyanatobutanal **1c** at RT and using methanol as solvent. Removal of solvent at RT and scratching the remaining thick mass with ethyl acetate:methanol (5:1) gave a solid product which was washed with chilled methanol to give the condensation product **9** in 38% yield. Attempts to purify the left-over reaction mixture by carrying out column chromato-graphy over silica gel did not give any identifiable product. IR (KBr) spectrum of **9** shows absorption bands at 3360 and 3241 (NH, OH) and 1649 cm^{-1} (C=N). GCMS of **9** gave M^+ ion peak at *m/z* 347 (5%). ^{1}H NMR of **9** reported in the experimental section of this paper fully supports the structure assigned to N,N-bis-(6-hydroxy-4-methyl-2-thioxo-tetrahydro-pyrimidin-1-yl)-guanidine (**9**, **Scheme I**)

Biological results

Compounds **2** and **9** at 50 mg/kg p.o and **4**, **6**, **7** and **8** at 100 mg/kg p.o were tested for anti-inflammatory

Table I — Anti-inflammatory and analgesic activity evaluation of compounds **1, 2, 4, 6-9**.

Compd mg/kg p.o.	Dose activity %	Anti-inflammatory mg/kg p.o.	Dose activity %	Analgesic
1	NT	NT	100	75
			50	25
2	50	12	50	11
4	100	19	100	25
6	100	18	100	50
7	100	13	100	50
8	100	18	100	75
9	50	16	50	15
Ibuprofen	100	66	100	75
			50	50

activity in the carrageenin induced paw oedema model[29] and the results are summarized in **Table I**. Compounds **2**, **4** and **6-9** showed 12,19,18,13,18 and 16% anti-inflammatory activity respectively. Ibuprofen, a standard drug exhibited 66% anti-inflammatory activity at 100 mg /kg p.o.

Compounds **1**, **2**, **4** and **6-9** on analgesic activity evaluation (**Table I**) using phenylquinone writhing assay[30] exhibited 75 and 25% (100 mg and 50 mg/kg p.o.); 11% (50 mg/kg p.o.); 25, 50, 50, 75 (100 mg/kg p.o.) and 15% (50 mg/kg p.o.) analgesic activity respectively. Ibuprofen, a standard drug exhibited 75% and 50% analgesic activity at 100 and 50 mg/kg p.o. respectively.

Experimental Section

Melting points (m.p.) 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 Bruker WH-500, 300, and 200 spectrometers at *ca*, 5-15% (w/v) solutions in DMSO-d_6 or $CDCl_3$ (TMS as internal standard). FAB-MS was recorded on Jeol SX-120 (FAB) spectrometer. GCMS was recorded on a Perkin Elmer Clarus 50 mass spectrometer. Elemental analysis was carried on Vario EL III elementor. Thin layer chromatography (TLC) were run 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 Qualigens silica gel for column chromatography (60-120 mesh).

Synthesis of 3, 3, 4a-trimethyl decahydrobenzo [4, 5] imidazo [1, 2-*c*]pyrimidin -1-thione, 1. 1, 2-Diaminocyclohexane (0.230 mL, 2 mmol) was taken in methanol (10 mL) and to it was added 4-isothiocyanato-4-methylpentan-2-one (0.32 mL, 2 mmol). The reaction contents were allowed to stand at RT for 1 day. The solid product which separated out was filtered and washed with chilled methanol to give the pure condensed product **1**. Yield 303 mg (60%). m.p. 245°C; IR (KBr): 3212 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6): δ 1.14-1.38 (m + 3s, 13H, 3×CH_3 + 2×CH_2), 1.63-1.66 (d, 1H, one H of pyrimidine -CH_2-), 1.72-1.76 (m, 2H, CH_2), 1.90-1.92 (d, 1H,-CH-), 2.15-2.18 (d, 1H, one H of pyrimidine -CH_2-), 2.71-2.74 (d, 1H, -NH-, exch), 2.80-2.89 (m, 2H, -CH_2-), 3.25-3.27 (d, 1H, -CH-), 7.72 (s, 1H, -NH- exch); GC-MS: *m/z* (%) 253 (M^+,38.15), 238 (M^+- CH_3, 66.99), 220 (M^+- SH, 26.67), 195 (M^+-NCS, 2.65), 179 (*m/z* 238- HSCN, 28.03), 139 ($C_8H_{15}N_2^+$, 28.62), 138 ($C_8H_{14}N_2^{\cdot+}$, 7.19), 137 ($C_8H_{13}N_2^+$, 10.63), 123 ($C_7H_{11}N_2^+$, 9.80), 97 ($C_6H_{11}N^{\cdot+}$, 18.20), 96 ($C_6H_{10}N^+$, 33.60), 82 ($C_6H_{10}^{\cdot+}$, 24.35), 81($C_6H_9^+$, 51.20). Anal. Calcd. for $C_{13}H_{23}N_3S$: C, 61.66; H, 9.09; N, 16.60; S, 12.64. Found: C, 61.89; H, 9.11; N, 16.57; S, 12.49%.

Synthesis of 3-methyl-decahydrobenzo[4, 5] imidazo [1,2-*c*] pyrimidine-1-thione, 2. 1,2-Diaminocyclohexane (0.230 mL, 2 mmol) was taken in methanol (10 mL) and to it was added 3-isothiocyanatobutanal (0.26 mL, 2 mmol). The *p*H of reaction contents was adjusted to about 4 by adding a few drops of 10% H_2SO_4 in methanol. The reaction contents were heated under reflux for 10 hr and then the 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 and purified by recrystallization from methanol to give pure **2**. Yield

225 mg (50%). m.p. 250°C; IR (KBr): 3203 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6): δ 1.06-1.29 (m, 7H, 3H of CH_3 and 4H of 2×CH_2), 1.29 -1.37 (m, 1H, CH), 1.50 (m, 2H, -CH_2-),1.71-1.74 (m, 2H, CH_2), 1.90-2.30 (m, 2H), 2.79-2.90 (m, 2H), 3.00-3.11 (m, 2H, -CH_2-), 4.20-4.35 (m,1H,NH-CH-N), 7.83 (s, 1H, NH, exch.), 8.06 (s, 1H, NH exch); GC-MS: *m/z* (%) 225 (M^+, 100), 192 (M^+-SH, 80.29), 124 ($C_7H_{12}N_2^{\cdot+}$,8.39), 123 (*m/z* 124-H, 17.24), 82 ($C_6H_{10}^{\cdot+}$, 30.06), 81($C_6H_9^+$, 76.22). Anal. Calcd. for $C_{11}H_{19}N_3S$: C, 58.66; H, 8.44; N, 18.66; S, 14.22. Found: C, 58.29; H, 8.80; N, 18.36; S, 14.08%.

Synthesis of 2, 2, 11a,-trimethyl-1, 2, 3, 11a, -tetrahydro-11-oxa -3, 4a- diaza- benzo [*b*]fluorene-4-thione, 3. 3-Amino-2-naphthol (0.318 g, 2 mmol) was dissolved in methanol (30 mL) by warming and then cooled to RT. To the cooled solution was added 4-isothiocyanato-4-methylpentan-2-one (0.320 mL, 2 mmol). The reaction contents were allowed to stand at RT for 2 days. No solid product separated out. The solvent was removed under reduced pressure and the crude product so obtained was purified by column chromatography over silica gel. Elution with $CHCl_3$:ethyl acetate (9:1) gave the pure product **3**. Yield 240 mg (40%). m.p.155°C; IR (KBr): 3436 (NH), 1595 cm^{-1} (Ar); ^{1}H NMR (DMSO-d_6): δ 1.27 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.98-2.08 (d, 1H, one H of pyrimidine -CH_2-), 2.18-2.22 (d, 1H, one of H pyrimidine -CH_2-), 7.19 (s, 1H, Ar), 7.28-7.31 (m, 2H, Ar), 7.38 (s, 1H, Ar), 7.66-7.74 (m, 2H, Ar), 7.81 (s, 1H, NH, exch); FAB-MS: *m/z* (%) 299 (MH^+, 5), 283 (M^+- CH_3, 100), 184($C_{12}H_{10}NO^+$, 70). Anal. Calcd. for $C_{17}H_{18}N_2OS$: C, 68.45; H, 6.04; N, 9.39; S, 10.73. Found: C, 68.31; H, 5.82; N, 9.21; S, 10.49%.

Synthesis of 7a, 9, 9, -trimethyl-7a, 8, 9, 10-tetrahydro-7-oxa-10, 11a-diaza-benzo [*c*] flourene-11-thione, 4. 1-Amino-2-naphthol hydrochloride (0.392 g, 2 mmol) was dissolved in methanol (20 mL) and to it was added 4-isothiocyanato-4-methylpentan-2-one (0.320 mL, 2 mmol). The reaction contents were allowed to stand at RT for 4 days. No solid product separated out. The solvent was removed under reduced pressure and the crude product so obtained was purified by column chromatography over silica gel. Elution with ethyl acetate: methanol (7:3) gave the pure product **4**. Yield 298 mg (50%). m.p.175°C; IR (KBr): 3415 (-NH-), 1559 cm^{-1} (Ar); ^{1}H NMR (DMSO-d_6): δ 1.28 (s, 3H, CH_3), 1.52 (s, 6H, 2×CH_3), 1.92-2.13 (dd, 2H, -CH_2- of pyrimidine ring), 7.35-7.45 (m, 2H, Ar), 7.50-7.65 (m, 2H, Ar), 7.85-8.05 (m, 2H, Ar), 9.70 (bs, 1H, NH, exch); GC-MS: *m/z* (%) 298 (M^+, 5.70), 297 (M^+-H,100), 184($C_{12}H_{10}NO^+$),2.37), 183($C_{12}H_9NO^{\cdot+}$, 8.52). Anal. Calcd. for $C_{17}H_{18}N_2OS$: C, 68.45; H, 6.04; N, 9.39; S, 10.73. Found: C, 68.32; H, 5.87; N, 9.71; S, 11.02%.

Synthesis of 3,3,4a-trimethyl-1-thioxo-2,3,4,4a-tetrahydro-1*H*-5-oxa-2, 12b-diaza-benzo[a]anthracen-6-one, 5. 3-Amino-2-naphthoic acid (0.187 g, 1 mmol) was dissolved in methanol (10 mL) and to it was added 4-isothiocyanato-4-methylpentan-2-one (0.16 mL, 1 mmol). The reaction mixture was heated under reflux for 24 hr and then the solvent was removed under reduced pressure. The crude product so obtained was purified by column chromatography over silica gel. Elution with $CHCl_3$:ethyl acetate (1:1) gave the pure product **5**. Yield 170 mg (52%). m.p. 210°C; IR (KBr): 3398 (-NH-), 1725 (ester), 1534 cm^{-1} (Ar); ^{1}H NMR (DMSO-d_6 + $CDCl_3$): δ 1.38 (s, 3H, -CH_3), 1.46 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 2.25-2.29 (d, 1H, one H of pyrimidine -CH_2-), 2.47-2.52 (d, 1H, one H of pyrimidine -CH_2-), 6.82 (s, 1H, NH, exch), 7.48-7.55 (m, IH, Ar), 7.88-7.97 (m, 3H, Ar), 8.30 (s, 1H, Ar), 8.61 (s, 1H, Ar); FAB-MS: *m/z* (%) 327 (MH^+, 80); 268 (MH^+-HSCN; 10). Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.25; H, 5.52; N, 8.58; S, 9.81. Found: C, 66.52; H, 5.39; N, 8.63; S, 9.74%.

Condensation of 1, 3-diamino-2-hydroxypropane with 4-isothiocyanato-4-methylpentan-2-one, 6, 7. 1,3-Diamino-2-hydroxypropane (0.180 g, 2 mmol) was taken in methanol (10 mL) and to it was added 4-isothiocyanato-4-methylpentan-2-one (0.63 mL, 4 mmol). The reaction mass was allowed to stand at RT for 2 days and then the solvent was evaporated at RT. To the semi-solid residue left behind was added ethyl acetate:diethyl ether (5:1) and scratched. The solid product separated out was filtered and washed with chilled methanol to give the product **6** *i.e*. 1,3-bis(6-hydroxy-4,4,6-trimethyl-2-thioxo-tetrahydro-pyrimidin-1-yl)propan-2-ol. Yield 202 mg (25%). m.p. 210°C; IR (KBr): 3308 and 3190 cm^{-1} (-NH-, -OH); ^{1}H NMR (DMSO-d_6 + D_2O): δ 1.34 (s, 12H, 4×CH_3), 1.57 (s, 6H, 2×CH_3), 1.91-1.95 (d, 2H, CH_2), 2.10-2.15 (d, 2H, CH_2), 2.77 (m, 1H,-CH-), 3.15-3.19 (d, 2H, -CH_2- N), 3.38-3.43 (d, 2H, -CH_2-N); GCMS: *m/z* (%) 404 (M^+, 31.67), 387 (M^+ -OH, 17.22), 346 (M^+- NCS; 4.66); Anal. Calcd. for $C_{17}H_{32}N_4O_3S_2$: C, 50.49; H, 7.92; N, 13.86; S, 15.84. Found: C, 50.73; H, 7.81; N, 13.93; S, 15.77%. The filtrate of **6** was subjected to column chromatography over silica gel. Elution with $CHCl_3$ gave pure product **7** *i.e* 7,7,8a-trimethyl-2-((4,4,6-trimethyl-2-thioxo-

3,4-dihydropyrimidin-1(2*H*)-yl)-methyl)-hexahydro-oxazolo[3,2-f]pyrimidine-5-thione. Yield 295 mg (40%). m.p. 215 °C; IR (KBr): 3416 and 3215 cm^{-1} (-NH-, -NH-); ^{1}H NMR (DMSO-d_6+ $CDCl_3$): δ 1.25 (s, 6H, 2×CH_3), 1.34 (s, 6H, 2×CH_3), 1.52 (s, 3H, CH_3), 1.83-1.88 (d, 1H, one H of pyrimidine -CH_2-), 2.00 (s, 3H, -.CH_3), 2.13-2.17 (d, 1H, one H of pyrimidine -CH_2-), 3.48 -3.55 (t, 1H, one H of-CH_2-), 3.55-4.17 (m, 1H, -CH-) 4.27-4.33 (m, 1H, one H of -CH_2-), 4.75 (s + m, 2H, one H of CH_2 + one olefinic H), 4.87-4.90 (q, 1H, one H of -CH_2-), 7.71 (bs, 1H, NH, exch) 8.00 (bs, 1H, NH, exch). FAB MS: *m/z* (%) 369 (MH^+, 100), 368 (M^+, 40), 335 (M^+-·SH, 10), 213 ($C_{10}H_{17}N_2SO^+$, 80). Anal.Calcd. for $C_{17}H_{28}N_4OS_2$: C, 55.43; H, 7.60; N, 15.21; S, 17.39. Found: C, 55.19; H, 7.72; N, 15.11; S, 17.47%.

Synthesis of 3, 3, 4a, 7, 7, 8a-hexamethyl-2, 3, 4, 4a, 7, 8, 8a, 10- octahydro-6*H*-2, 4b, 4c, 6, 9, 10, 10a-heptaazaindeno [1, 2-*a*] indene-1, 5- dithione, 8. 1,3-Diaminoguanidine monohydrochloride (0.250 g, 2 mmol) was taken in methanol (20 mL) and to it was added 4 isothiocyanato-4-methylpentan-2-one (0.63 mL, 4 mmol). The reaction mass was allowed to stand at RT for 4 days and then the solvent was allowed to evaporate at RT. The semi solid residue left behind was triturated with ethyl acetate:methanol (2:5) but no pure product could be obtained and so the whole crude product was subjected to column chromatography over silica gel. Elution with ethyl acetate:methanol (9:1) gave the pure product **8**. Yield 260 mg (35%). m.p. 170°C; IR (KBr): 3207 (NH), 1653 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6 + $CDCl_3$): δ 1.31 (s, 6H, 2 ×CH_3), 1.39 (s, 6H, 2×CH_3), 1.55 (s, 6H, 2×CH_3), 1.92-2.04 (d, 2H, CH_2), 2.10-2.15 (d, 2H, -CH_2-), 5.52 (s, 1H, NH, exch), 6.81 (s, 1H, NH, exch), 8.30 (s, 1H, NH, exch). FABMS: *m/z* (%) 368 (MH^+, 25), 352 (M^+-, ·CH_3 30). Anal. Calcd. for $C_{15}H_{25}N_7S_2$: C, 49.04; H, 6.81; N, 26.70; S, 17.43. Found: C, 49.30; H, 7.12; N, 26.43; S, 17.22%.

Synthesis of N,N-bis-(6-hydroxy-4-methyl-2-thioxotetrahydro-pyrimidin-1-yl) guanidine, 9. 1,3-Diaminoguanidine monohydrochloride (0.250 g, 2 mmol) was taken in methanol (20 mL) and to it was added 3-isothiocyanatobutanal (0.52 mL, 4 mmol). The reaction mass was allowed to stand at RT for 3 days and then the solvent was allowed to evaporate at RT. The crude product left behind was scratched with ethyl acetate:methanol (5:1) and the solid product thus separated out was filtered and washed with chilled methanol to give pure product **9**. Yield 265 mg (38%). m.p. 240°C; IR (KBr): 3360 and 3241 (-NH-, -OH), 1649 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6 + $CDCl_3$): δ 1.22-1.24 (d, 6H, 2×CH_3), 1.60 -1.72 (q, 2H, -CH_2-), 2.28-2.32 (m, 2H, -CH_2-), 3.62 (m, 2H, 2× >CH-OH), 4.67-4.69 (m, 2H, 2×>CH-CH_3), 6.08 (s, 2H, 2×-OH, exch), 8.63 (s, 1H, NH, exch), 10.01 (s, 2H, 2×NH, exch.), 10.93 (s, 2H, 2×NH, exch); GC-MS: *m/z* (%) 347 (M^+, 5). Anal. Calcd. for $C_{11}H_{21}N_7O_2S_2$: C, 38.44; H, 6.05; N, 27.95; S, 18.44. Found: C, 38.30; H, 6.00; N, 27.82; S, 18.29%.

The filtrate of **9** left behind was subjected to column chromatography over silica gel. Elution with different solvent mixtures did not yield any identifiable product and hence it was discarded.

Anti-inflammatory activity Screening

Anti-inflammatory activity evaluation[29] 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 apponeurosis. The volume of the paw was measured plethysmographically immediately and 3 hr 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**, **2**, **4** and **6-9** screened are reported under Results and Discussion.

Analgesic activity screening

Analgesia was measured by the writhing assay[30] using Swiss mice (15-20g). Female mice were screened for writhing on day-1 by injecting intraperitonially 0.2 mL 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 5 in each group and showing significant writhing were given orally a 25, 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 using the following formula:

Protection = 100-[{No. of writhings for treated mice)/(No. of writhings for untreated mice)}×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**, **2**, **4** and **6-9** were screened for analgesic activity and results are reported under Results and Discussion.

Conclusion

A number of condensed pyrimidine derivatives **1-9**, have been synthesized and characterized by spectroscopic means and elemental analysis. These compounds have been screened for anti-inflammatory and analgesic activity. Compounds **1** and **8** exhibit good analgesic activity whereas other compounds exhibit moderate anti-inflammatory and analgesic activity.

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