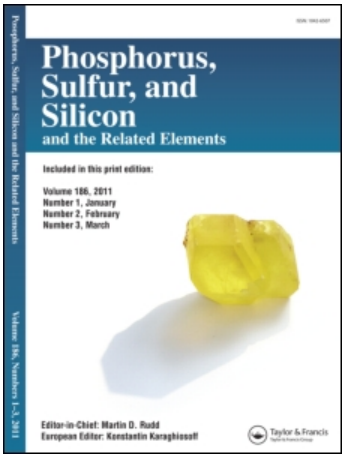


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# ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY EVALUATION OF HETEROCYCLIC COMPOUNDS SYNTHESIZED BY THE REACTION OF 4-ISOTHIOCYANATO-4 METHYL-2-PENTANONE WITH AMINES

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# ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY EVALUATION OF HETEROCYCLIC COMPOUNDS SYNTHESIZED BY THE REACTION OF 4-ISOTHIOCYANATO-4-METHYL-2-PENTANONE WITH AMINES

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The reaction of 4-isothiocyanato-4-methyl-2-pentanone with 1,2-diaminoanthraquinone at reflux temperature in methanol using catalytic amount of sulphuric acid (pH ~ 1) gave pyrimidoanthraquinonimidazole (**I**). Pyrimidonaphthoimidazole (**II**) was prepared by $SnCl_2$/HCl reduction of nitropyrimidine thiol (to give **II'**) and subsequent cyclization by refluxing in methanol containing catalytic amount of acid. 4-Nitro-1,2-phenylenediamine on treatment with 4-isothiocyanato-4-methyl-2-pentanone in methanol at room temperature gave a mixture of 1-(2'-amino-5'-nitrophenyl)-4, 4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy pyrimidine -2(3H)thione and 1-(2'-amino-5'-nitrophenyl)-4',4,6-trimethyl-1,4,5,6- tetrahydro-6-methoxy pyrimidine-2(3H) thione (**III**). Compound **III** undergo cyclization on refluxing in methanol using sulphuric acid as a catalyst to give cyclized compound **III'**. 2-Aminopyridine on reaction with 4-isothiocyanato-4-methyl-2-pentanone at room temperature in methanol gave 1-(2'-pyridine)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6- hydroxy pyrimidine -2(3H)thione (**IV**) whereas the same reaction at reflux temperature and using catalytic amount of sulphuric acid (pH ~ 4) gave 1-(2'-pyridine) -4,4,6-trimethyl-1,4-dihydro-pyrimidine-2(3H)thione (**V**). The reaction of 4-isothiocyanato-4-methyl-2-pentanone with 3-aminopropanol at reflux temperature using methanol as a solvent gave pyrimido-oxazine thione (**VI**) however when the same reaction was done using 1.1 mole equivalent of sulphuric acid, the product isolated was found to be S-methyl pyrimido-oxazine (**VII**). When ethylenediamine was treated with 4-isothiocyanato-4-methyl-2-pentanone under reflux temperature in methanol at pH ~ 9, pyrimidoimidazole (**VIII**) was obtained but when the same reaction was carried out at room temperature, a complex mixture was obtained which on chromatographic separation gave only a minor compound i.e. 1-(2'-aminoethyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxypyrimidine-2(3H)thione (**IX**). 1,2-Diaminopropane on condensation with 4-isothiocyanato-4-methyl-2-pentanone at pH ~ 5 and at

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reflux temperature in methanol gave pyrimidoimidazole (**X**) in good yield. Out of the above synthesized compounds, **I–III**, **V–VIII** and **X** were screened for anti-inflammatory and analgesic activity at 100 mg/kg and 50mg/kg respectively. Compounds **I,II,III** and **VIII** showed 19, 19, 25 and 10% anti-inflammatory activity respectively whereas compounds **V–VII** and **X** were found to be inactive. Except compound **III** which showed mild (60%) analgesic activity, all other compounds were found to be inactive.

*Keywords:* Amines; isothiocyanatopentanone; anti-inflammatory; analgesic; NMR; HRMS; heterocyclic



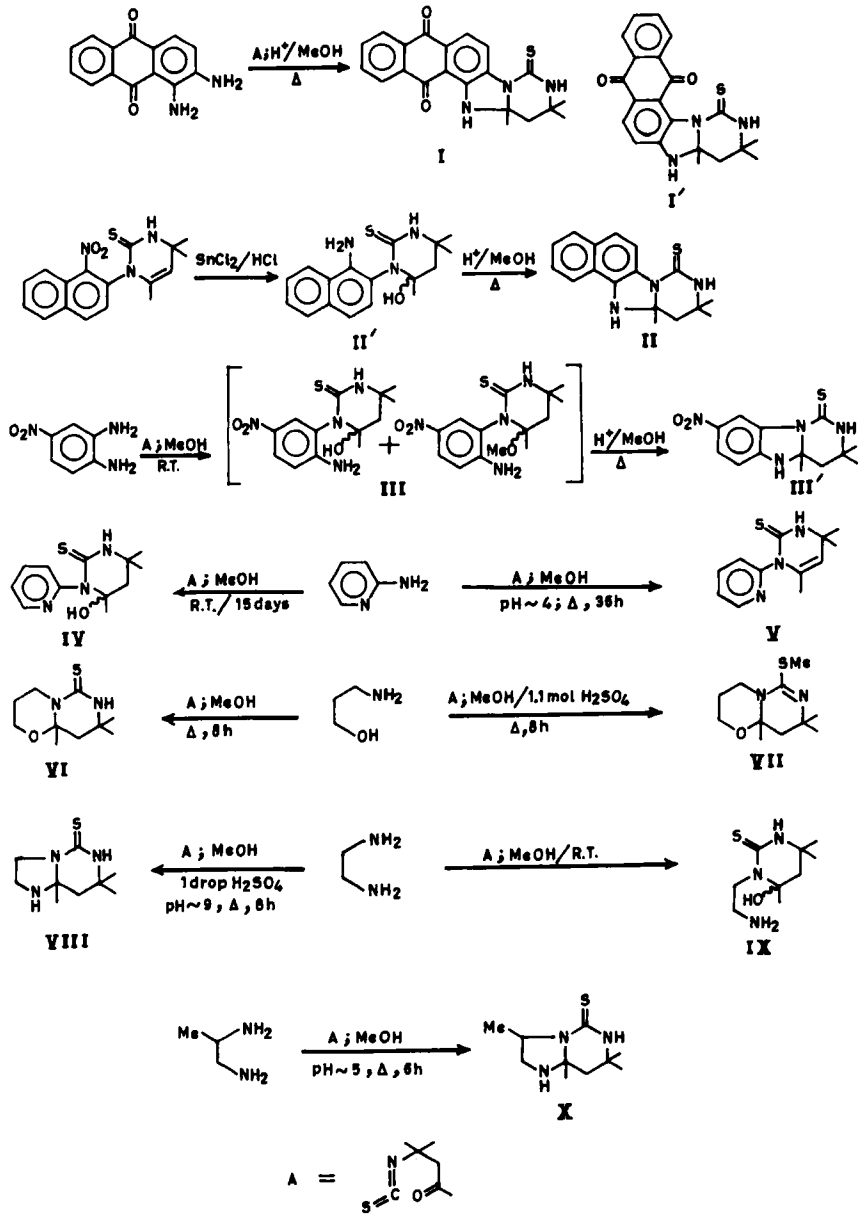
## INTRODUCTION

There are many non steroidal anti-inflammatory drugs such as aspirin, phenylbutazone, oxyphenbutazone, indomethacine, ibuprofen, ketoprofen etc. available in the market. These drugs have ulcerogenic activity as a side effect[1]. Pyrimidobenzimidazole derivatives[2,3] have been reported in literature as anti-rheumatic agents and gastric acid secretion inhibitors. Large number of papers published on this subject every year indicates the need and importance for the synthesis and development of safer anti-inflammatory drugs. In continuation[4–8] of our efforts towards this direction we wish to report the synthesis and anti-inflammatory as well as analgesic activity evaluation of some heterocyclic compounds containing N & S.

## RESULTS AND DISCUSSION

The reactions of 4-isothiocyanato-4-methyl-2-pentanone with amines have been reported at reflux temperature of toluene or xylene[9]. We have studied the reaction of 4-isothiocyanato-4-methyl-2-pentanone with 1,2-diaminoanthraquinone, 4-nitro-1,2-phenylenediamine, 2-aminopyridine, 3-aminopropanol, ethylenediamine and 1,2-diaminopropane under acidic conditions/at room temperature and in certain cases different reaction products were obtained depending on the reaction conditions (Scheme-I).

When 1,2-diaminoanthraquinone was condensed with 4-isothiocyanato-4-methyl-2-pentanone under reflux conditions using methanol as a solvent and using catalytic amount of sulphuric acid (pH $\sim$ 1), pyrimidoanthraquinonimidazole (**I**) was obtained. The $^1$H NMR (300 MHz; DMSO-$d_6$) show a doublet at $\delta$ 8.9 (d, 1H, Ar) showing that aromatic proton at lowest field (8.9 ppm, deshielded[8] by the near C = S function) is a doublet (due to ortho coupling), this rules out the isomeric structure **I'** (where there is no aromatic proton near C = S function). HRMS of **I** gave $M^+$ ion peak at 377.11910 ($M^+$, 55.18) Calc. for




SCHEME 1

$C_{21}H_{19}N_3SO_2$ 377.11981. 1,4-dihydro-4,4,6-trimethyl-1-(1′-nitro-2′-naphthyl)-pyrimidine-2(3H) thione was prepared by the method reported in literature[10]. $SnCl_2$/HCl reduction[7] of thione gave hydroxy pyrimidine **II′**, which when

heated under reflux in methanol using catalytic amount of sulphuric acid gave pyrimidonaphthoimidazole (**II**). The structure of **II** was confirmed by $^1$H NMR and HRMS reported in Table - I. The reaction of 4-isothiocyanato-4-methyl-2-pentanone with 4-nitro-1, 2-phenylenediamine at room temperature gave a mixture of 1-(2′-amino-5′-nitrophenyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy pyrimidine- 2(3H)thione and 1-(2′-amino-5′-nitrophenyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-methoxypyrimidine-2(3H)thione (**III**) which was evident from $^1$H NMR spectrum of **III**. $^1$H NMR spectrum of **III** (300 MHz; DMSO-$d_6$) show a singlet at δ 3.15 (-$OCH_3$) accounting for about one and half proton and a singlet at 6.0 (-OH, exch.) accounting for half proton indicating that **III** is a mixture of hydroxy and methoxy pyrimidines. This product could not be purified due to labile nature of -OH & -$OCH_3$. HRMS of **III** show $M^+$ ion peak at 324.12602 ($M^+$, 23.71) Calc. for $C_{14}H_{20}N_4SO_3$ 324.12561. The product **III** when heated under reflux in methanol using sulphuric acid as catalyst (pH ~ 3) undergo cyclization giving previously reported product pyrimidobenzimidazole[8] (**III′**). 2-Aminopyridine on treatment with 4-isothiocyanato-4-methyl-2-pentanone in methanol at room temperature gave 1-(2′-pyridine) -4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy-pyrimidine-2 (3H)thione (**IV**) in 5% yield only. The $^1$H NMR (300 MHz; DMSO-$d_6$) spectrum of **IV** accounts for all the protons i.e: δ 1.4 (2s, 6H, $CH_3$ + $CH_3$), 1.70 (s, 3H, $CH_3$), 2.2(d, 1H, one H of -$CH_2$-), 2.30 (d, 1H, one H of-$CH_2$-), 7.0 (m, 2H, Ar), 7.5(s, 1H, -OH, exch.), 7.8 (m, 1H, Ar), 8.2(d, 1H, Ar), 9.4(s, 1H, $-\overset{\overset{S}{\|}}{C}-NH-$ exch.). HRMS of **IV** does not give $M^+$ ion peak but $M^+$-HSCN peak was observed at 192.12646 (20.94%). When the same reaction i.e. condensation of 4-isothiocyanato-4-methyl-2-pentanone with 2-aminopyridine at pH ~ 4 under reflux condition using methanol as a solvent was carried out, the product obtained was 1-(2′-pyridine)-4,4,6-trimethyl-1,4-dihydropyrimidine-2(3H)thione (**V**). The structure of **V** is supported by $^1$H NMR and HRMS (Table - I). $^1$H NMR of **V** (300 MHz; DMSO-$d_6$) show a singlet at δ4.80 accounting for one proton corresponding to >C = CH-. When 4-isothiocyanato-4-methyl-2-pentanone was treated with 3-aminopropanol under reflux condition using methanol as a solvent, the product obtained was a well known pyrimido oxazine thione[9] (**VI**). The structure of **VI** is supported by correct $^1$H NMR and HRMS. However when the same reaction was carried out in the presence of 1.1 mole equivalent of sulphuric acid, S-Methyl derivative of **VI** i.e. **VII** was obtained in good yield. In this case sulphuric acid must have generated methyl carbonium ion in situ which act as an electrophile and sulphur being a good nucleophile attack on $\overset{+}{C}H_3$ and thus generating S-Methyl product i.e. **VII**. The structure of **VII** is supported by $^1$H NMR

TABLE I Physical constants and spectral data of various compounds

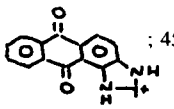
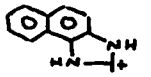
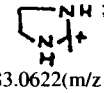
| *pound* | *Solvent of Cryst.* | *mp °C* | *Yield %* | *$^1$H NMR (300 MHz; DMSO-$d_6$): δppm* | *Mass Spectral data m/z (rel.int.)* |
|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | 6 |
| | MeOH | 276 | 67 | 1.2(s, 3H; $CH_3$), 1.4(s, 3H; $CH_3$), 1.6(s, 3H; $CH_3$), 2.20(d, 1H; one H of -$CH_2$-), 2.60(d, 1H; one H of -$CH_2$-), 7.5(d, 1H; Ar), 7.90(m, 2H; Ar), 8.2(m, 2H; Ar), 8.9(d, 1H; Ar), 9.1(s, 1H, -NH-exch.) S ‖ 9.3(s, 1H, -C-NH-exch.). | 377.11910($M^+$, 55.18) Calcd. for $C_{21}H_{19}N_3SO_2$ 377.11981.362.09555($M^+$-$CH_3$; 94.96), 303.11311($M^+$-($CH_3$+HSCN); 100.00)263.08117 (  ; 45.69), 262.07439, (m/z 263.08117-H; 60.78 261.06713(m/z 262.07439-H; 7.00). |
| | MeOH/THF | 222 | 50 | 1.3(s, 3H; $CH_3$), 1.4(s, 3H; $CH_3$), 1.5(s, 3H; $CH_3$), 2.25(d, 1H; one H of -$CH_2$-), 2.45(d, 1H; one H of -$CH_2$-), 7.05(s, 1H; -NH-exch.), 7.2(d, 1H; Ar), 7.4 S ‖ (m, 1H; Ar), 7.8(d, 2H, Ar), 8.45(s, 1H, -C-NH-exch.), 9.05(d, 1H; Ar). | 297.12953($M^+$, 85.58) Calcd. for $C_{17}H_{19}N_3S$ 297.12997, 296.12112($M^+$-H; 4.30), 282.10643($M^+$-$CH_3$; 73.14), 237.139101 (m/z 296.12112-HSCN; 13.31), 223.12354 ($M^+$-($CH_3$ + HSCN), 100.00), 183.09095 (  ;42.20), 182.0 (m/z 183.09095-H; 83.58), 181.0767 (m/z 182.08409-H; 29.01). |

TABLE I (con't)

| | | | | |
|---|---|---|---|---|
| MeOH | 180–85 | 50 | 1.1–1.5(m, 9H; $CH_3$ + $CH_3$ + $CH_3$), 1.9(d, 1/2H), 2.1(d, 1/2 H), 2.3(d, 1/2 H), 2.4(d, 1/2 H), 3.15(s, 1.50 H), 6.0(s, 1/2 H exch.), 6.6(m, 3H; 1H, Ar + 2H, $-NH_2$ exch.), 7.90(m, 2H; Ar), 8.6(s, 1/2 H; exch-NH-), 8.85(s, 1/2H; exch.-NH-). | 324.12602($M^+$, 23.71) Calcd. for $C_{14}H_{20}N_4SO_3$ 324.12561, 292.09950($M^+$ $CH_3OH$, 43.59). |
| MeOH | 120 | 5 | 1.4(2s, 6H; $CH_3$ + $CH_3$), 1.70(s, 3H; $CH_3$), 2.2 (d, 1H; one H of $-CH_2-$), 2.3(d, 1H; one H of $-CH_2-$), 7.0(m, 2H; Ar), 7.5(s, 1H; -OH exch.), 7.8(m, 1H; Ar), 8.2(d, 1H; Ar), 9.4(s, 1H; -C(=S)-NH-exch.). | 192.12646($M^+$-HSCN, 20.94), 133.07661 ($C_8H_9N_2$, 9.33) |
| $CHCl_3$/EtOAc | 100 | 30 | 1.7(s, 6H; $CH_3$ + $CH_3$), 1.85(s, 3H; $CH_3$), 4.80(s, 1H; > C=CH-), 7.1(dd, 1H; Ar), 7.2(m, 1H; Ar), 8.0 (m, 1H, Ar), 8.5(d, 1H; Ar), 10.7(s, 1H; exch., -C(=S)-NH-). | 174.11537($M^+$-HSCN, 14.36), 159.09274 (m/z 174.11537-$CH_3$; 100.00). |
| MeOH | 170 | 60 | 1.15(s, 3H; $-CH_3$), 1.25(s, 3H; $CH_3$), 1.55(m + s, 4H; $CH_3$ + 1H), 1.70(m, 1H), 2.00(s, 2H; $-CH_2-$ of pyrimidine ring), 3.35(dt, 1H), 3.70(dd, 1H), 4.0(dt, 1H), 5.2(dd, 1H), 8.30(s, 1H; -C(=S)-NH-exch.). | 214.1143($M^+$, 100.00) Calcd. for $C_{10}H_{18}$ 214.1146, 213.1064($M^+$-H; 2.19), 199.09 ($M^+$-$CH_3$; 47.55), 154.1234(m/z 213.106 HSCN; 1.43), 140.1083(m/z 199.0917-HS 31.66). |
| Pet. ether | 50 | 40 | 1.2(2s, 6H; $CH_3$ + $CH_3$), 1.4(m, 1H), 1.50(s, 3H; $CH_3$), 1.80(d, 1H), 1.90(m, 2H), 2.35(s, 3H; $-SCH_3$), 3.5(dt, 1H), 3.80(m, 1H), 4.0(m, 2H). | 228.12944($M^+$, 71.75) Calcd. for $C_{11}H_{20}$ 228.12964, 213.10622($M^+$-$CH_3$, 97.29), 183.09539(m/z 213.10622-$CH_2O$; 13.42), 140.10733(m/z 213.10622-$CH_3SCN$; 32.61), 114.03772($C_5H_8NS$, 100.00) |

TABLE I (con't)

| | | | | | |
|---|---|---|---|---|---|
| I | THF | 220 | 60 | 1.1–1.25(3s, 9H, 3 × $CH_3$), 1.6(d, 1H; Jgem = 15Hz, one H of -$CH_2$-), 2.1(d, 1H; Jgem = 15 Hz, One H of -$CH_2$- of pyrimidine ring), 3.0(m, 3H; $CH_2$ + NH, one H exch.), 3.4(m, 1H), 3.65(m, 1H), 7.85(s, 1H; -C(=S)-NH-,exch.). | 199.1141($M^+$, 100.00) Calcd. for $C_9H_{17}N_3S$ 199.1139, 184.0911($M^+$-$CH_3$; 85.62), 157.0799-(m/z 184.0911-HCN; 40.26), 125.1076(m/z 184.0911-HSCN; 90.66), 85.0772(  ;4<br>84.0732 (m/z 85.0772-H; 49.03), 83.0622(m/z 84.0732 -H; 26.46). |
| | EtOAC/Pet. ether | 110 | 1 | After $D_2O$ exch.:- 1.1(s, 3H; $CH_3$), 1.2(s, 3H; $CH_3$), 1.4(s, 3H; $CH_3$), 1.95(dd, 2H, -$CH_2$- of pyrimidine ring), 2.9(m, 1H), 3.10(m, 1H), 3.80(m, 1H), 4.15(m, 1H). | 217.12504($M^+$, 1.82) Calcd. for $C_9H_{19}N_3SO$, 217.12488, 199.11434($M^+$-$H_2O$, 4.95). |
| | THF/MeOH | 192 | 40 | 1.1–1.26(3s + 1d, 12H; 4× $CH_3$), 1.80(d, 1H; one H of -$CH_2$- of pyrimidine ring), 2.10(d, 1H; one H of -$CH_2$- of pyrimidine ring), 3.1(m, 3H), 3.6(m, 1H), 7.9(s, 1H-C(=S)-NH-). | |



pounds **I, II, IV–X** reported in this table gave elemental analysis for C, H and N within ±0.4%.

KBr) $cm^{-1}$: Compound **III** 3500(-$NH_2$, -OH), 1620(Ar); Compound **VI** 3189(-NH-); Compound **VIII**, 3200(-NH-).

and HRMS as reported in Table-I. Diaminoethane on condensation with 4-isothiocyanato-4-methyl-2-pentanone under reflux in methanol using one drop of sulphuric acid as a catalyst (pH ~ 9) gave a known imidazopyrimidine thione[9] (**VIII**). The structure of **VIII** was supported by $^1$H NMR & HRMS (Table - I). When the diaminoethane was allowed to react with 4-isothiocyanato-4-methyl-2-pentanone in methanol at room temperature, the product obtained was a complex mixture. By using column chromatography we could isolate only 1-(2′-aminoethyl)-4, 4, 6-trimethyl-1, 4, 5, 6-tetrahydro- 6 -hydroxy pyrimidine 2(3H) thione (**IX**) as a minor product. The structure of **IX** is confirmed on the basis of $^1$H NMR & HRMS reported in Table -I. The reaction of 1,2-diamino-propane with 4-isothiocyanato-4-methyl-2-pentanone at room temperature in methanol gave a complex mixture however when the same reaction was carried out at pH ~ 5 and at reflux temperature in methanol, a clean product **X** was obtained in good yield. The structure of **X** is supported by $^1$H NMR (300 MHz; DMSO—$d_6$) spectrum i.e. δ1.1–1.26 (3s + 1d, 12H, 4x$CH_3$), 1.80 (d, 1H; one H of -$CH_2$- of pyrimidine ring), 2.1 (d, 1H, one H of - $CH_2$- of pyrimidine ring), 3.1(m, 3H), 3.6(m, 1H), 7.9 (s,1H,C(=S)-NH-).

From all the reactions mentioned in scheme-I, it is clear that 4-isothiocyanato 4-methyl-2-pentanone gave reaction conditions dependent reaction products. Physical constants and spectral data for all the compounds **I–X** (Scheme-I) are summarized in Table-I.

Compounds **I–III**, **V–VIII** and **X** were tested for anti-inflammatory and analgesic activity at 100mg/kg and 50 mg/kg respectively. Compounds **I,II,III** and **VIII** showed 19, 19, 25 and 10% anti-inflammatory activity respectively where as compounds **V–VII** and **X** were found to be inactive. Compounds **I, II, V–VII** and **X** did not show any analgesic activity where as compound **III** showed mild (60%) analgesic activity.

## EXPERIMENTAL

Melting points, determined on a JSGW apparatus are uncorrected. Only principal sharply defined IR peaks are reported. $^1$H NMR spectra were recorded on approximately 5–15%(w/v) solutions in appropriate deuterated solvents with tetramethyl silane as internal standard. Line positions are recorded in ppm from the reference. The MS spectrometer peak measurements were made by comparison with perflurotributylamine at a resolving power of 15,000. TLC was performed by using silica gel G for TLC (Merck) and spots were visualized by

Iodine vapour or by irradiation with U.V. light 254nm. Silica gel (60–120mesh) was used for column chromatography.

## Synthesis of Pyrimidoanthraquinonimidazole (I)

1,2-Diaminoanthraquinone (238 mg, 1m mol) was dissolved in hot methanol (300 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (0.25 ml; 1.5 m mol) and one drop of conc. sulphuric acid. The pH of the reaction medium was ~1. The reaction mixture was heated under reflux for 8 h. and then solvent was removed under reduced pressure. The residue left behind was basified with sodium carbonate solution. The solid so obtained was filtered, washed with water and crystallized from methanol to give pyrimidoanthraquinonimidazole (**I**). Yield 250mg (67%).



## Synthesis of Pyrimidonaphthoimidazole (II)

1,4-dihydro-4,4,6-trimethyl-1-(1′-nitro-2′-naphthyl) pyrimidine -2(3H)thione[10] was reduced by $SnCl_2$/HCl to afford hydroxy pyrimidine[7] (**II′**). Yield, 60%, m.p. 227(d), solvent of crystallization methanol.

Hydroxy pyrimidine (**II′**) (0.315 gm, 0.001 mol) was dissolved in methanol (50ml) and to it was added a drop of sulphuric acid and the reaction contents were heated under reflux for 4h. Solvent was removed under reduced pressure and the residue left behind was basified with sodium carbonate solution. The solid residue left behind was filtered, washed with water and air dried. The crude product so obtained was crystallized from methanol/THF, to give pyrimidonaphthoimidazole (**II**). Yield 150mg (50%).

## Reaction of 4-Isothiocyanato-4-Methyl-2-Pentanone with 4-nitro-1,2-Phenylenediamine (III)

4-Nitro-1,2-phenylene-diamine (1.53g; 0.01 mol) was dissolved in 100 ml methanol by heating and then reaction contents were cooled to room temperature and to it was added 4-isothiocyanato-4-methyl-2-pentanone (1.73 ml; 0.011 mol). Reaction contents were allowed to stand at room temperature for two days when a yellow solid started separating out. The reaction contents were transfered in a beaker and solvent was allowed to evaporate at room temperature. The solid so obtained was washed thoroughly with methanol to give condensed product **III**. Yield 1.6gm (50%).

Condensed product **III** (1.0gm) was taken in 100 ml methanol and heated to boil and then 3 drops of sulphuric acid (pH ~ 3) were added and the reaction contents were heated under reflux for 8 h. Solvent was removed under reduced pressure and the residue left behind was basified with sodium carbonate solution and filtered. Washed the solid compound with water and air dried. The crude product so obtained was crystallized from methanol to give **III'**. Yield 800 mg., m.p. 250°C. $^1$H NMR spectrum was superimposable with authentic sample reported[8] earlier.

## Synthesis of 1(2'-Pyridine)-4,4,6-Trimethyl-1,4,5,6-Tetrahydro-6-Hydroxy Pyrimidine-2(3H)Thione (IV)

2-Aminopyridine (1.88gm; 0.02mol) was dissolved in methanol (20ml) and to this solution was added 4-isothiocyanato-4-methyl-2-pentanone (3.14ml; 0.02 mol). The reaction contents were left at room temperature for 15 days. Solvent was removed under reduced pressure and syrup like residue left behind was subjected to column chromatography over silica gel. Elution with $CHCl_3$ and then with ethyl acetate gave oily material which was discarded. Further elution with methanol gave a solid product which was recrystallized from methanol to give **IV**. Yield 0.25gm (5%)



## Synthesis of 1(2'-Pyridine)-4,4,6-Trimethyl-1,4-Dihydropyrimidine-2(3H)Thione (V)

2-Aminopyridine (1.88 gm, 0.02 mol) was dissolved in methanol (20ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (3.45 gm; 0.022 mol) and a drop of sulphuric acid (pH ~ 4). Reaction contents were heated under reflux for 36 h. Solvent was removed under reduced pressure and the crude syrup like material left behind was subjected to column chromatography over silica gel. Elution with chloroform: ethyl acetate (8 : 2) gave a solid product which was crystallized from chlorofom/ethyl acetate to give condensed product **V**. Yield 1.40gm (30%).

## Condensation of 4-Isothiocyanato-4-Methyl-2-Pentanone with 3-Amino Propanol (VI)

3-Aminopropanol (3ml; 0.04 mol) was taken in methanol (20 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (6.28 ml; 0.04 mol). The reaction contents were heated under reflux for 8 h. and solvent was removed under

reduced pressure. The crude product so obtained was crystallized from methanol to give pyrimido oxazinethione (**VI**). Yield 5.13 gm (60%), m.p. 170°C (Lit. 183°C)[9].

### Synthesis of S-methyl Pyrimido Oxazine (VII)

3-Aminopropanol (3ml; 0.04 mol) was added to methanol (40ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone(6.3ml; 0.04 ml) and conc sulphuric acid (2.3 ml). Reaction mixture was heated under reflux for 9 h. and then solvent was removed under reduced pressure. Liquid residue left behind was basified with sodium carbonate solution and then extracted with ethyl acetate. Organic layer was washed with water and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure and thick syrup like residue left behind was subjected to column chromatography over silica gel. Elution with pet ether gave white crystalline product (**VII**), yield 3.6gm (40%).



### Synthesis of Imidazopyrimidine Thione (VIII)

Ethylenediamine (1.2 ml; 0.02 mol) was added to methanol (20ml) and to it was added 4-isothiocyanato-4-methyl-2- pentanone (3.2ml; 0.02 mol) and sulphuric acid (0.4ml) (pH ~ 9.0). Reaction mixture was heated under reflux for 8h. Solid product separated out during refluxing. Solvent was removed under reduced pressure and the solid so obtained was washed with sodium carbonate solution and then with water. The crude product was crystallized from THF to give **VIII**. Yield 2.40 gm(60%), m.p. 220°(d) (Lit. 251°C)[9].

### Reaction of 4-Isothiocyanato-4-Methyl-2-Pentanone with Ethylenediamine (IX)

4-Isothiocyanato-4-methyl-2-pentanone (3.2 ml, 0.02 mol) was added to methanol (10ml) and to this solution was added ethylenediamine (1.2ml; 0.02mol) dropwise so that the temperature of the reaction mixture does not increase more than 20°C. The reaction mixture was allowed to stand over night at room temperature and then methanol was removed under reduced pressure. The solid so separated was washed with methanol to give white solid. The $^1$H NMR spectrum of this solid was very complex showing it to be a complex mixture. The crude product was subjected to column chromatography over silica gel. Elution with chloroform: ethyl acetate (8 : 2) gave some side product, further elution with ethyl acetate gave a white solid on removal of solvent. This white solid was

washed with pet ether to give pure 1-(2′-aminoethyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy pyrimidine 2(3H) thone (**IX**). Yield 44mg (1%).

## Condensation of 1,2-Diaminopropane with 4-Isothiocyanato-4-Methyl-2-Pentanone (X)

1,2-Diaminopropane (1.50 ml;0.02 mol) was added to methanol (60ml) and to this solution was added 4-isothiocyanato-4-methyl-2-pentanone(4.70 ml, 0.03 mol). The pH of the reaction mixture was adjusted at ~5 by adding a few drops of conc sulphuric acid. The reaction contents were heated under reflux for 6h. Solvent was removed under reduced pressure and the residue left behind was basified with sodium carbonate solution. Solid so obtained was filtered, washed with water and air dried. The crude product so obtained was crystallized from THF/methanol to give compound **X**. Yield 1.7 gm(40%).



## Anti-Inflammatory Activity Testing[11]

Anti-inflammatory activity testing was carried out using carrageenin-induced oedema in albino rats: The oedema in one of the hind paws was induced by injection of 0.1 ml of 1% carrageenin solution into planter aponeurosis. The volume of the paw was measured plethysmo-graphically immediately after and 3h. 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 the compound treated groups was calculated and compared with the group receiving standard drug. At 100 mg/kg p.o.none of the compounds possessed potent anti-inflammatory activity. However compounds **I, II, III** and **VIII** inhibited the carrageenin induced hind paw oedema by 19, 19, 25 and 10% respectively as compared to the standard drug, phenylbutazone which showed 35% activity at 30 mg/kg p.o.

## Analgesic Activity Testing[12]

Analgesia was measured by hot plate test using Swiss mice (15–20g) bred in animal house of Central Drug Research Institute and maintained under standard laboratory conditions. The test required determination of reaction time to noxious heat stimulus to mouse placed on heated plate, thermostatically maintained at 56 ± 0.5°C. The basal reaction time was determined twice at 10 min. interval and averaged to obtain single pre-drug latency. The end point used in these experiments was licking or raising of the front or hind paw or an attempt to

jump off the plate. An increase in the reaction time by 75% or more was indicative of analgesic state of animal. However a cut off time of 10 seconds was used to avoid damage to the paw tissue. The test compound was administered intraperitoneal in 50 mg/kg dose. The reaction time was determined every 10 minutes till it was near the pre-drug level. Percent of animals exhibiting analgesia and duration of analgesic effect was determined. None of the tested compounds (**I–III, V–VIII** and **X**) showed potent analgesic activity. However compound **III** exhibit mild (60%) analgesic activity.

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