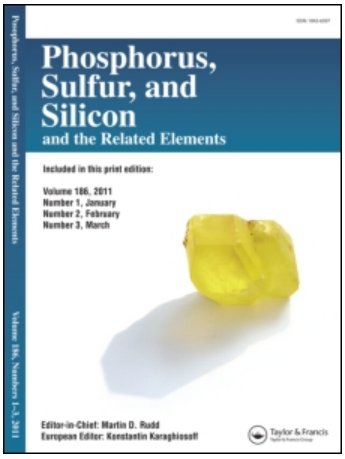

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SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY EVALUATION OF SOME ACRIDINYL AMINO ANTIPYRINE, ACRIDINYL AMINO ANTHRAQUINONE, ACRIDINO THIOUREA AND THIAZOLINO THIOUREA DERIVATIVES

S. M. Sondhi[a]; Vinay K. Sharma[a]; Nidhi Singhal[a]; R. P. Verma[a]; R. Shukla[b]; R. Raghubir[b]; M. P. Dubey[b]
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SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY EVALUATION OF SOME ACRIDINYL AMINO ANTIPYRINE, ACRIDINYL AMINO ANTHRAQUINONE, ACRIDINO THIOUREA AND THIAZOLINO THIOUREA DERIVATIVES

S.M. SONDHI[a*], VINAY K. SHARMA[a], NIDHI SINGHAL[a], R.P. VERMA[a], R. SHUKLA[b], R. RAGHUBIR[b] and M.P. DUBEY[b]

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9- Chloro – 2(substituted) – acridines (**I**) on condensation with 4 – amino antipyrine, 1-amino anthraquinone and 2 – amino anthraquinone gave corresponding condensed products **II, III** and **IV**. Phenyl isothiocyanate reacts with 9 – amino – 2 or 4 (substituted)-acridines (**V**) and iminothiazolines (**VII**) to give corresponding N-phenyl -N'- substituted thioureas **VI** and **VIII** in good yield. Anti-inflammatory activity screening for **IIa, b, III, IV, VIb** and **VIIIa – I** was carried out at 100 mg / kg p.o. and compounds **IV, VIIIa, VIIIb** and **VIIIg-k** showed 12, 12,14,18,7,23,13 and 18% activity whereas all others were found to be inactive. Analgesic activity screening for **IIb, III** and **IV** was carried out at 100mg/kg p.o.Only compound **III** showed 25% activity whereas **IIb** and **IV** were found to be inactive.

Keywords: Acridinyl derivatives; acridino thiourea; thiazolino thiourea; antiinflammatory activity; NMR; HRMS

INTRODUCTION

Ulcerogenic activity[1] continue to be an undesirable side effect of a group of non steroidal antiinflammatory and analgesic drugs such as aspirin, phenyl butazone, oxyphenylbutazone, indomethacin, ibuprofen and ketopro-

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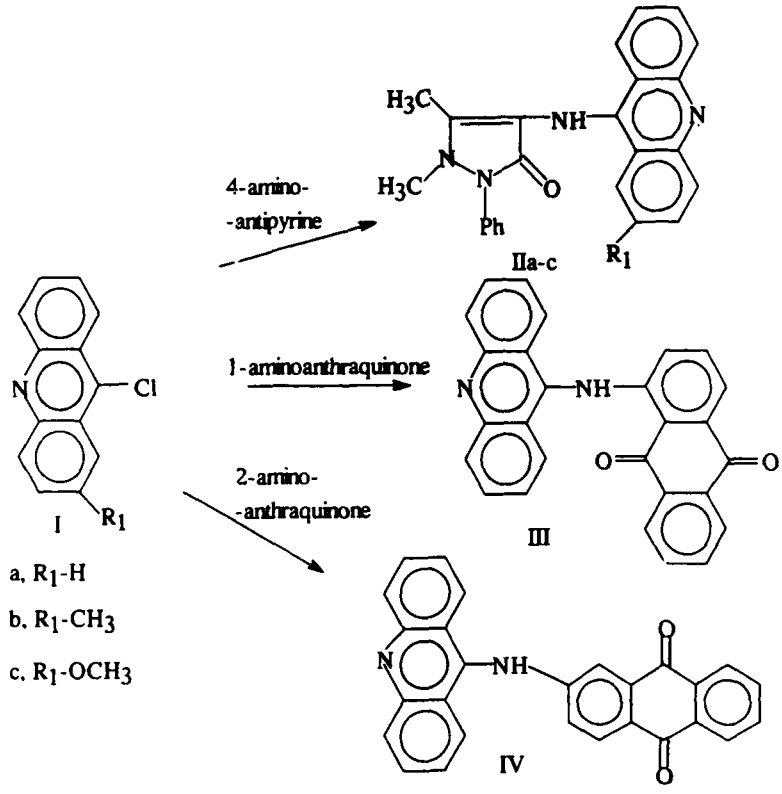
fen available in the market for symptomatic relief from inflammation. Acridine derivatives exhibiting fungicidal[2–4], antimicrobial[5–6], antiparasitic[7], antibacterial[8], antimalarial[8], antitumor[9–15] and antiinflammatory activities[16] are reported in literature. In continuation of our efforts in search of potential antiinflammatory compounds[17–23] and ultimately in the development of safer antiinflammatory drugs we wish to report synthesis, antiinflammatory and analgesic activity evaluation of a number of acridine (**II, III, IV, VI**) and thiazoline derivatives (**VIII**) (Scheme –1 & 2).

RESULTS AND DISCUSSION

The required 9-chloro acridines (**Ia-c**) were synthesized by the condensation of N-arylanthranilic acids[24] with phosphorus oxychlorides[25]. 9-Chloroacridine, 9-chloro-2-methyl acridine and 9-chloro-2- methoxy – acridine (**Ia – c**) on condensation with 4-aminoantipyrine in methanol under reflux for 13 hrs followed by purification by chromatography over silica gel gave corresponding acridinyl amino antipyrine **IIa, IIb** and **IIc** respectively (Scheme 1). Yield, m.p.,and spectral data of **IIa-c** is reported in Table I. 1-Aminoanthraquinone and 2-amino anthraquinone on condensation with 9-chloroacridine (**Ia**) in DMF and heating at 120–130°C for eight hours gave corresponding condensation products **III** and **IV** which were purified by crystallization to give pure **III** and **IV** (Scheme 1). HRMS of both **III** and **IV** gave M^+ ion peaks at 400.12038 and 400.12000 respectively. Spectral data, yield, m.p. and solvent of crystallization for both **III** and **IV** are reported in Table I.

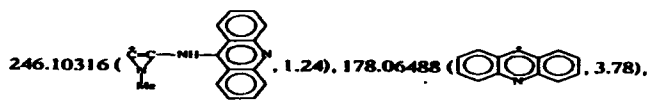
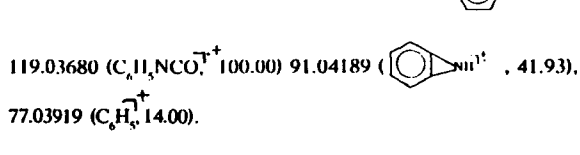
9-Amino-2-methyl acridine and 9-amino-4-methyl acridine (**Va – b**) were synthesized from corresponding 9 – chloroacridines by following the procedure reported in literature[25]. 9- Amino-2 or 4 (substituted) acridines (**Va – b**) were dissolved in methanol and allowed to react with phenyl isothiocyanate at room temperature to give corresponding N – phenyl - N'-acridinyl thioureas (**VIa – b**). (Scheme- 2) Spectral data, yield, m.p. and solvent of crystallization of **VIa -b** are reported in Table-1. 3,4 – Diaryl – 2-iminothiazolines (**VIIa – l**) were prepared by the condensation of phenacyl thiocyanate and amine hydrochlorides as reported in literature[26]. Thiazolines (**VIIa -l**) were dissolved in methanol and to it was added phenyl isothiocyanate and allowed to react at room temperature to give corre-

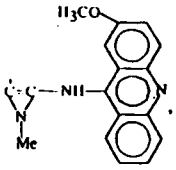


SCHEME I

sponding thioureas (Scheme- 2) (**VIIIa – l**) in good yields. All the thioureas (**VIIIa – l**) were characterised by spectroscopic methods and spectral data along with yield, m.p. and solvent of crystallization are reported in Table-1. On antiinflammatory activity evaluation of **IIa, b, III, IV, VIa-b, VIIIa – e** and **VIIIg – l** at 100 mg /kg p.o. **IV, VIIIa-b** and **VIIIg-k** showed 12, 12, 14, 18, 7, 23, 13 and 18% activity respectively whereas all other compounds were found to be inactive. Compounds **IIb, III**, and **IV** were screened for analgesic activity at 100 mg /kg. p.o., only **III** exhibited 25% analgesic activity and others (**IIb** and **IV**) were found to be inactive.

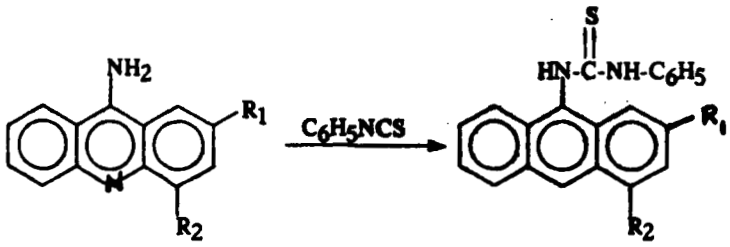
TABLE I Physical constants and spectral data of various compounds

*Solvent of ryst./elution**	*Yield %*	*m.p. °C*	*Spectral data. ^1H NMR (DMSO – d_6) δ ppm. IR (γ max) cm^{-1}. Selected bands.. HRMS (m/z; relt. Int.)*
2	*3*	*4*	*5*
thylacetate : leOH (5:5)*	30	220	^1H NMR (300 MHz). 2.35 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 7.30(q. 3H, Ar), 7.60 (t, 4H, Ar), 8.05 (m, 4H, A (d, 2H, Ar), 11.00 (bs, 1H, – NH-, Exch.). IR.3269 & 3154 (-NH-), 1644 (-C-N), 1484 (Ar). HRMS 380. 1 (M^+, 16.45) Calcd for $C_{24}H_{20}N_4O$ 380.16370, 261.12570 (M^+- C_6H_5NCO, 2.82), 260.11877 (261. 12570-H  **246.10316 (, 1.24), 178.06488 (, 3.78),** **119.03738 ($C_6H_5NCO^{\cdot+}$, 2.44), 56.05006 ($C_3H_6N^+$, 100.00).**
thylacetate : leOH (5:5)*	87	210 (d)	^1H NMR (300MHz).2.40 (2s, 6H, CH_3+CH_3), 3.25 (s, 3H, H_3C-N<) 7.35 (m, 3H, Ar), 7.50 (m, 3H, Ar), 1H, Ar), 7.95 (m, 2H, Ar), 8.05 (d, 1H, Ar), 11.00 (bs, I H, -NH-, exch). IR. 3364 & 3250 (-NH-), 1588 (- 1485 & 1433 (Ar). HRMS 394.17733 (M^+, 31.68), Calcd. for  $C_{25}H_{22}N_4O$ 394.179.35, 274.13339, (43.16), 119.03680 ($C_6H_5NCO^{\cdot+}$ 100.00) 91.04189 (, 41.93), 77.03919 ($C_6H_5^+$, 14.00).

*Solvent of cryst./elution**	*Yield %*	*m.p. °C*	*Spectral data. ^1H NMR (DMSO – d_6) δ ppm. IR (γ max) cm^{-1}. Selected bands.. HRMS (m/z; relt. Int.)*
2	*3*	*4*	*5*
thylacetate : leOH (5:5)*	50	175	^1H NMR (200MHz) 2.40 (s, 3H,-CH_3), 3.25 (s, 3H, H_3C-N<), 3.90 (s, 3H, -OCH_3), 7.30 (m, 3H, Ar), 7.50 Ar), 7.75 (dd, 1H, Ar) 8.05 (m, 4H, Ar), 8.65 (d, 1H, Ar), 10.50 (bs, 1H,-NH-,exch,). HRMS 410.17386 (M^+,28.15) calcd. for $C_{25}H_{22}N_4O_2$ 410.17429 291.13418 (M^+-C_6H_5NCO; 3.57), 290.12845 (291.13418 - H, 5.83), 276.11291 ( . 3.81), 119.03722 ($C_8H_5NCO^{\cdot+}$, 2.26).
leOH	47	290	^1H NMR (200MHz) 7.15 (m, 3H, Ar), 7.50 (m, 4H, Ar), 7.80 (m, 4H, Ar), 8.20 (m, 4H, Ar), 11.70 (s, 1H, exch.). HRMS, 400.12038 (M^+, 0.35) Calcd. for $C_{27}H_{16}N_2O_2$ 400.12119, 372.1250 (M^+-CO;2.06).
leOH	67	262	^1H NMR (200MHz) 6.90 (dd, 1H, Ar), 7.25 (m, 3H, Ar), 7.50 (dd, 2H, Ar) 7.90 (m, 5H, Ar), 8.20 (m, 4H 11.75 (s, 1H, -NH-, exch.). HRMS. 400.12000 (M^+, 0.74) Calcd. for $C_{27}H_{16}N_2O_2$ 400.12119, 372.12769 CO; 2.02).
tyl acetate: leOH (5:5)*	9	>240	^1H NMR (200MHz) after D_2O exchange. 2.20 (s, 3H, -CH_3), 7-8.3(m, 12H,Ar). HRMS does not give M^+i but gave M^+-H_2S ion peak at 309.12593 (M^+-H_2S, 32.00), 208.09962 (M^+-C_6H_5NCS; 100.00).
HF/ MeOH	30	160	^1H NMR (400MHz) 2.60 (s,3H,-CH_3), 7.0 (bs, 1H, Ar) 7.30 (m, 6H, Ar) 7.55 (d, 1H, Ar) 7.70 (t, 1H, Ar), 1H, Ar) 8.05 (d, 1H, Ar) 8.15 (d 1H, Ar), 10.70 (bs, 2H, 2x – NH-, exch). IR. 3149(-NH-) 1558 & 1496 (HRMS does not give M^+ion peak but gave M^+-H_2S peak at 309.12364 (M^+-H_2S, 3.65), 208.09861 (M^+-C_6H_5NCS, 100.00), 135.01339 ($C_8H_5NCS^{\cdot+}$, 58.95).

*Solvent of ryst./elution**	*Yield %*	*m.p. °C*	*Spectral data. ^1H NMR (DMSO – d_6) δ ppm. IR (γ max) cm^{-1}. Selected bands.. HRMS (m/z; relt. Int.)*
2	*3*	*4*	*5*
HF	78	212	^1H NMR (200 MHz) 6.75 (bd, 3H, Ar) 7.0–7.50 (m, 13H, Ar), 10.05 (s, 1H,-NH-, exch.) IR. 3300 & 3200 1583 (C=N), 1468 (Ar), HRMS 387.08765 (M^+, 30.85) Calcd. for $C_{22}H_{17}N_3S_2$ 387.08640. 354.10792 (M 9.25), 295.03699 (M^+-C_6H_6N, 100.00).
HF	92	180	^1H NMR (200 MHz), 1.25 (t, 3H, -CH_3,) 3.90 (q, 2H, -CH_2-), 6.80 (m, 5H, Ar) 7.00 (s, 1H, >C=CH-), 7.20 Ar) 7.35 (m, 2H, Ar), 7.50 (d, 3H, Ar), 10.10 (s, 1H,-NH-, exch.) IR 3212 (-NH-), 1590 (-C=N-), 1474 (A
HF	90	180	^1H NMR (200M Hz) 3.60 (s, 3H, -OCH_3), 6.85 (m, 3H, Ar), 7.0 (t, 1H, Ar), 7.25 (m, 10H, Ar), 7.50 (t, H 10.10 (s, 1H,-NH-, exch). IR. 3222 (-NH-), 1594 (-C=N-) 1473 (Ar).
HF	82	190	^1H NMR (200MHz), 1.80 (s, 3H, -CH_3), 2.20 (s, 3H, -CH_3), 6.80 (bs, 3H, Ar) 7.20 (m, 11H, Ar), 10.20 (s, -NH-, exch). MS 416 (M^++1, 4.2), 415 (M^+, 13.4), 323 (M^+-C_6H_6N, 100.00).
HF	90	225	^1H NMR (200 MHz) 6.85 (d, 5H, Ar), 7.25 (m, 6H, Ar), 7.80 (m, 3H, Ar), 8.20 (d, 1H, Ar), 10.20 (s, 1H, exch). IR 3246 & 3163 (- NH-), 1595 (-C=N-), 1476 (Ar).
HF	80	222	^1H NMR (300M Hz) 3.70 (s, 3H,- OCH_3), 6.80 (m, 5H, Ar), 7.05 (s, 1H, —C=CH-), 7.30 (m, 4H, Ar), 7. 2H, Ar), 7.50 (m, 3H, Ar), 10.00 (s, 1H, -NH-, exch.). IR. 3251 & 3148 (-NH-), 1590 (-C=N-), 1506 & 14 HRMS. 417.09714 (M^+29.35) Calcd. for $C_{23}H_{19}N_3S_2O$ 417.09695. 384.11717 (M^+-SH, 9.89) 325.04847 (M^+-C_6H_6N 100.00) 282.08200 (M^+-C_6H_5NCS, 50.02), 135.01540 (C_6H_5NCS, 45.49).
HF / MeOH	95	185	^1H NMR (200MHz) 2.35 (s, 3H; CH_3), 6.81 (bs, 3H, Ar) 7.09 (s. 1H, = CH-S-), 7.25 (bs + d; 11H; Ar), 10 1H,-NH; exch.) IR 3231 (-NH-), 1594 (-C=N-) 1485 (Ar) HRMS. 401.10113 (M^+; 17.17) Calcd.for $C_{23}H_{1}$ 401.10205, 309.05111 (M^+-C_6H_6N; 100.00).
HF / MeOH	75	210	^1H NMR (200MHz) 6.85 (bs, 3H; Ar) 7.20 (m. 8H; Ar); 7.50 (dd, 4H, Ar); 10.14 (s,1H,-NH-; exch.) IR.32 3200 (-NH), 1591 (-C=N-), 1494 (Ar).
HF / MeOH	98	210	^1H NMR (200MHz) 2.00 (s, 3H, -CH_3); 6.90 (m,4H, Ar); 7.25 (m, 7H, Ar); 7.71 (m, 2H, Ar); 8.03 (d,1H, 10.30 (s, 1H,-NH-; Exch.) IR. 3285 & 3223 (-NH-); 1592 (-C=N); 1529& 1460 (Ar).
HF / MeOH	95	240	^1H NMR (200M Hz) 2.15 (s, 3H, -CH_3), 6.15 (m, 2H, Ar); 6.45 (m, 1H,Ar); 6.90 (d, 2H, Ar); 7.00 (d, 2H, 7.20 (d + s, 3H, Ar); 7.50 (m, 3H, Ar); 7.90 (d, 1H, Ar); 8.01 (m, 3H, Ar); 10.04 (s, 1H, -NH, exch). IR 32 (- NH-), 1591 (-C=N-) 1483 (Ar), MS 451 (M^+,7.1); 315 (M^+-C_7H_6NS, 100.00).

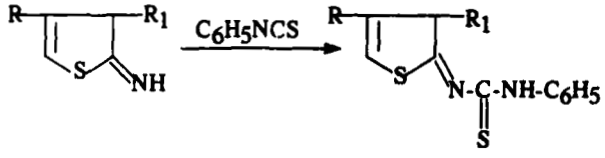
Solvent of Syst./elution[*]	*Yield %*	*m.p. °C*	*Spectral data. ^1H NMR (DMSO – d_6) δ ppm. IR (γ max) cm^{-1}. Selected bands.. HRMS (m/z; relt. Int.)*
2	*3*	*4*	*5*
THF / MeOH	85	200	^{1}H NMR (200MHz) 6.12 (t, 2H, Ar); 6.44 (t, 1H, Ar); 6.88 (d, 2H, Ar); 7.25 (m, 6H, Ar); 7.80 (m, 4H, A (d, 1H, Ar) 8.32 (d, 1H, Ar); 10.27 (s, 1H, -NH-, exch), IR 3234 (-NH); 1592 & 1443 (Ar).
THF / MeOH	70	242	^{1}H NMR (200MHz) 6.17 (t, 2H, Ar); 6.44 (t, 1H, Ar); 6.92 (d, 2H, Ar); 7.10–7.67(m, 8H, Ar); 7.87 (d, 1H 8.02 (t, 3H, Ar); 10.08 (s, 1H, – NH-, exch).



Va-b VIa-b

a, R_1=CH_3; R_2=H

b, R_1=H; R_2=CH_3



VIIa-l VIIIa-l

a, R = C_6H_5 ; R_1 = C_6H_5

b, R = (p) $C_2H_5OC_6H_4$; R_1 = C_6H_5

c, R = C_6H_5 ; R_1 = (o)$H_3COC_6H_4$

d, R = C_6H_5 ; R_1 = 1-(2,3-dimethylphenyl)

e, R = C_6H_5 ; R_1 = (o)O_2N-C_6H_4

f, R = (p) $H_3COC_6H_4$; R_1 = C_6H_5

g, R = C_6H_5 ; R_1 = (p)CH_3-C_6H_4

h, R = C_6H_5 ; R_1 = (p)Cl-C_6H_4

i, R = C_6H_5 ; R_1 = 1-(2-methyl-6-nitrophenyl)

j, R = (p) $H_3CC_6H_4$; R_1 = 2-naphthyl

k, R = C_6H_5 ; R_1 = 2(1-nitronaphthyl)

l, R = (p)BrC_6H_4 ; R_1 = 2-naphthyl

SCHEME 2

EXPERIMENTAL

Melting points determined on 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 tetramethylsilane as internal standard. Line positions are recorded in ppm from the reference. The MS spectrometer peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. TLC was performed by using silica get G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with UV light of 254 nm. Silica get (60 – 120 mesh) was used for column chromatography.

Condensation of 9-chloroacridine with 4-aminoantipyrine (II)

4–Aminoantipyine (609 mg; 3m mole) was dissolved in methanol (75 ml) and to it was added 9-chloroacridine (426 mg; 2 m mole). The reaction contents were heated under reflux for thirteen hours and then solvent was reduced to about 20 ml and the crude product was adsorbed over silica gel and purified by column chromatography over silica gel. Elution with chloroform, chloroform : ethylacetate (5:5) and ethylacetate removed side products and further elution with ethyl acetate : methanol (5:5) gave condensed product **IIa** which was washed with chloroform and air dried to give pure acridinyl aminoantipyrine (**IIa**). Yield 340 mg (42%). m.p. 220°C. Similarly condensation of **1b** & **1c** gave corresponding **IIb** & **IIc**. Yield, m.p., solvent of elution and spectral data of **IIa-c** are reported in Table I.

Condensation of 1 – aminoanthraquinone with 9 – chloroacridine (III)

1 - Aminoanthraquinone (454 mg; 2.0 m mole) was dissolved in DMF (10 ml) and to it was added 9-chloroacridine (426 mg, 2.0 m mole). The reaction contents were heated at 120 – 130°C for eight hours. The reaction contents were diluted with 5% sodium carbonate solution (100 ml). The solid so obtained was filtered, washed with water and then dissolved in 100 ml methanol and filtered. The filtrate was left over night. The solid separated out was filtered and filtrate was reduced to 5 ml volume and allowed to stand overnight. The solid separated out was filtered and

washed with cold methanol (2 ml) and air dried to give pure condensed product **III**. Yield 350 mg (47%) m.p. 290°C.

Similarly 2 - aminoanthraquinone was condensed with 9-chloroacridine to give product **IV**. Yield, m.p. and spectral data of **III** and **IV** are reported in Table I.

Condensation of 9 – aminoacridines (Va – b) with phenyl isothiocyanate. VIa – b

2-Methyl-9-aminoacridine (**Va**, 220 mg: 1 m mole) was dissolved in methanol (20 ml) and to it was added phenyl isothiocyanate (0.5 ml; 4 m mole). The reaction contents were allowed to stand at room temperature for five days and then solvent was removed under reduced pressure and the residue left behind was adsorbed on silica get and subjected to column chromatography over silica get. Elution with carbon tetrachloride, carbon tetrachloride : ethyl acetate (5: 5) and ethyl acetate removed side products, elution with ethyl acetate : methanol (5 : 5) gave pure condensed product **VIa**. Yield 9% m.p.>240°C.

In case of 4-methyl -9-amino acridine (**Vb**) the reaction contents were allowed to stand for 4 days and solid separated out was filtered, washed with methanol and recrystallized from THF / MeOH to give pure product **VIb**.

Yield, m.p., solvent of crystallization/clution and spectral data for **VIa-b** are reported in Table I.

Condensation of 3, 4 – diarylthiazolines (VIIa -l) with phenyl isothiocyanate (VIIIa -l)

3,4-Diaryl thiazoline [26] (**VIIa**, 252 mg; 1 m mole) was dissolved in methanol (20 ml) by heating and then cooled at room temperature and to it was added phenyl isothiocyanate (0.20 ml; 1.6 m mole) and the reaction contents were allowed to stand at room temperatue. A solid started separting out within one hour and the reaction contents were further allowed to stand for overnight. It was then filtered and washed with methanol to give condensed product **VIIIa** which was further purified by recrystallization. Similarly were prepared compounds **VIIIb – l**. Yield, m.p., solvent of crystallization and spectral data of all **VIIIa -l** are reported in Table I.

Antiinflammatory screening[27]

Antiinflammatory activity was carried out using carrageenin - induced paw oedema in albino rats obtained from animal facility of Central Drug Research Institute, Lucknow and maintained under standard laboratory conditions. The oedema in one of the hind paw was induced by injection of carrageenin (100 µl 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 the compound treated groups was calculated and compared with the group receiving standard drug. At 100mg /kg p.o. none of the compounds possessed potent antiinflammatory activity. However compounds **IV, VIIIa, VIIIb** and **VIIIg-k** showed 12, 12, 14, 18, 7, 23, 13 and 18% activity respectively as compared to the standard drug, phenylbutazone which showed 35% activity at 30 mg/ kg. p.o.

Analgesic activity screening[28]

Analgesia was measured by writhing assay using swiss mice (15 – 20 gm) bred in Animal House of Central Drug Research Institute, Lucknow and maintained under standard laboratory conditions. Female mice are screened for writhing on day 1 by injecting intraperitoneally 0.2 ml of 0.02% aqueous solution of phenyl quinone. They are kept on flat surface and number of writhes of each mice is recorded for 20 minutes. The mice showing significant writhes (>10) are sorted out and used for analgesic assay on following day. The mice consisting of 5 in each group and showing significant writhing were given orally 100 mg/kg p.o. dose of 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:

$$\%\text{Protection} = 100 - \left(\frac{\text{No. of writhing in treated}}{\text{No. of writhing in untreated}} \times 100\right)$$

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. None of the compounds **IIb, III**, & **IV** showed potent

analgesic activity. However compound **III** elicited mild (25%) analgesic activitiy.

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