Monatshefte für Chemie 131, 501–509 (2000)

Monatshefte für Chemie
Chemical Monthly

Synthesis and Antiinflammatory and Anticancer Activity Evaluation of Some Condensed Pyrimidines

Sham M. Sondhi[1,*], **Nidhi Singhal**[1], **Rajeshwar P. Verma**[1], **Sudershan K. Arora**[2], **Rakesh Shukla**[3], and **Ram Raghubir**[3]

[1] Department of Chemistry, University of Roorkee, Roorkee-247667, India
[2] Ranbaxy Research Laboratories, New Delhi-110020, India
[3] Division of Pharmacology, CDRI, Lucknow-226001, India

Summary. Upon condensation with 4-isothiocyanato-4-methyl-2-pentanone, 2,3-diaminonaphthalene and N-aminoethyladenosine gave in good yields substituted pyrimidonaphthoimidazole and imidazopyrimidine thione. Refluxing pyrimidobenzthiazole with methanol H_2SO_4 at $pH \sim 1$ resulted in S-methyl pyrimidobenzthiazole in moderate yield. Pyrimidobenzimidazole derivatives could be reacted to S-alkylated and N-acylated derivatives by refluxing with ethyl bromoacetate in the presence of anhydrous potassium carbonate in *THF* and by heating in an acetic acid/acetic anhydride mixture. Heating of pyrimidobenzimidazole with 75% aqueous H_2SO_4 on a water bath ended up in a rearranged product. All compounds gave correct ^{1}H NMR, IR, and HR mass spectra. Results of antiinflammatory, analgesic, and anticancer activity screening of the new compounds are described.

Keywords. Condensed pyrimidines; Antiinflammatory activity; Anticancer activity.

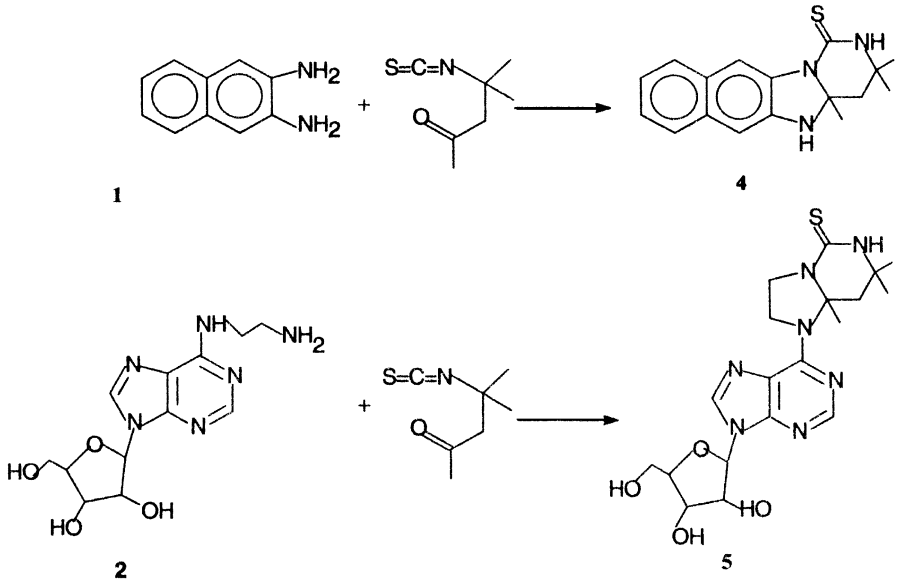
Introduction

Ulcerogenicity [1] is the major side effect of most non-steroidal antiinflammatory drugs (NSAID) used clinically; it has been reduced to a certain extent by modification of the carboxylic acid moiety [2]. As a result of better gastrointestinal tolerability, non-acidic non-steroidal antiinflammatory agents are increasingly favoured over acidic ones. Pyrazolo [1,5-*a*]pyrimidine [3] and pyrimidobenzimidazole derivatives [4, 5] have been reported as anti-rheumatic agents and gastric acid secretion inhibitors. In continuation of our efforts in search of potent antiinflammatory or biologically active molecules [6–14], we report the synthesis and biological evaluation of some condensed pyrimidines.

Results and Discussion

Condensation of 2,3-Diaminonaphthalene (**1**) with 4-isothiocyanato-4-methyl-2-pentanone either at reflux temperature of methanol and at $pH = 4$ or at room

* Corresponding author



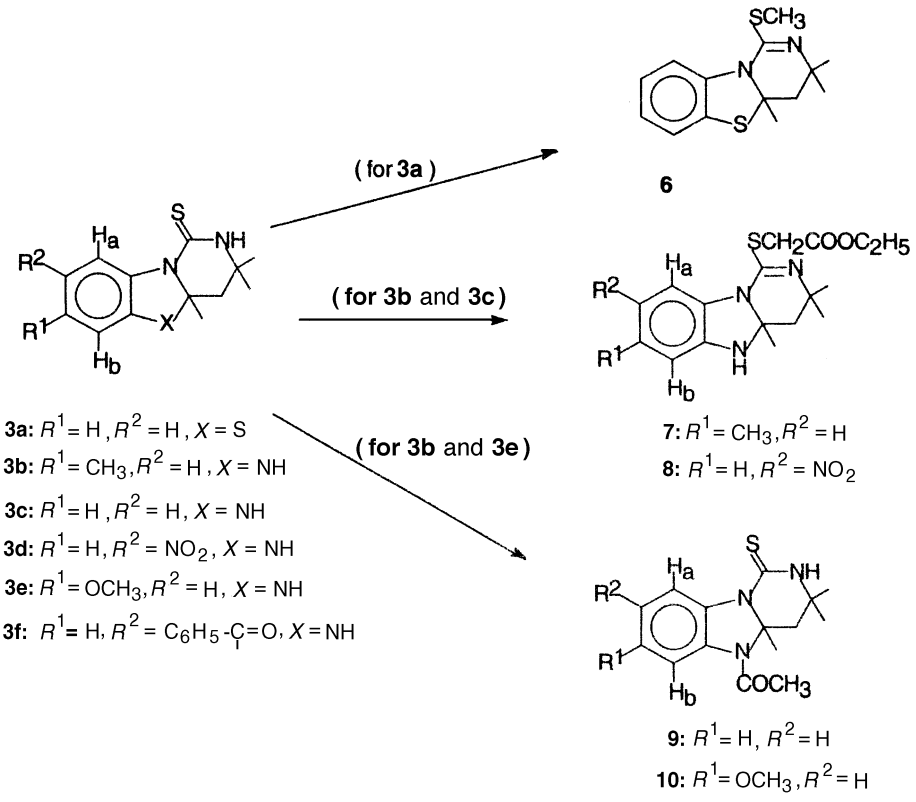
Scheme 1

temperature gave the pyrimidonaphthoimidazole **4** (Scheme 1); the yield of **4** was higher in the first case. N-Aminoethyladenosine (**2**) was prepared according to Refs. [16–17] and was condensed with 4-isothiocyanato-4-methyl-2-pentanone at room temperature to give the imidazopyrimidine thione derivative **5** (Scheme 1) in 92% yield. However if the same reaction was carried out in refluxing methanol at $pH \sim 5$, the yield was only 10%. The structures of **4** and **5** are supported by spectroscopic evidences.

Refluxing pyrimidobenzthiozole **3a** [10] in $MeOH/H_2SO_4$ acid ($pH \sim 1$) for eight hours and rendering the mixture alkaline after removing the methanol with sodium carbonate solution, gave the S-methyl derivative of pyrimidobenzthiazole **6** in 57% yield. ^{1}H NMR spectra [10] of **3a** show H_a as a doublet at $\delta = 8.55$ ppm which is due to the influence of the C = S double bond. In compound **6**, all aromatic protons are in the region of 7.10 to 7.50 ppm, indicating a high-field shift of H_a due to the conversion of >C=S to =C-SCH_3 and thus conforming that alkylation does take place at the >C=S moiety. The structure of **6** in supported by correct ^{1}H NMR and IR spectra as well as by HRMS.

Various pyrimidobenzimidazole derivatives were synthesized by substitution of pyrimidobenzimidazole and evaluated for their antiinflammatory activity in an effort to understand the effect of substitution. Pyrimidobenzimidazoles **3b**, **c** [9–10] on refluxing with ethyl bromoacetate in the presence of potassium carbonate using *THF* as solvent gave S-alkylated products **7** and **8** (Scheme 2). ^{1}H NMR spectra [9–10] show H_a at $\delta = 8.45$ and 9.50 ppm. After S-alkylation, these protons are shifted to high field (7.60 and 8.50 ppm). This observation indicates that ethyl bromoacetate reacts with the -C(=S)-NH- group of the pyrimidine ring and not with the NH-group of the imidazole ring.

Acetylation of **3d** and **3e** was carried out by refluxing with acetic anhydride/acetic acid to give the N-acetylated products **9** and **10** (Scheme 2). The ^{1}H NMR

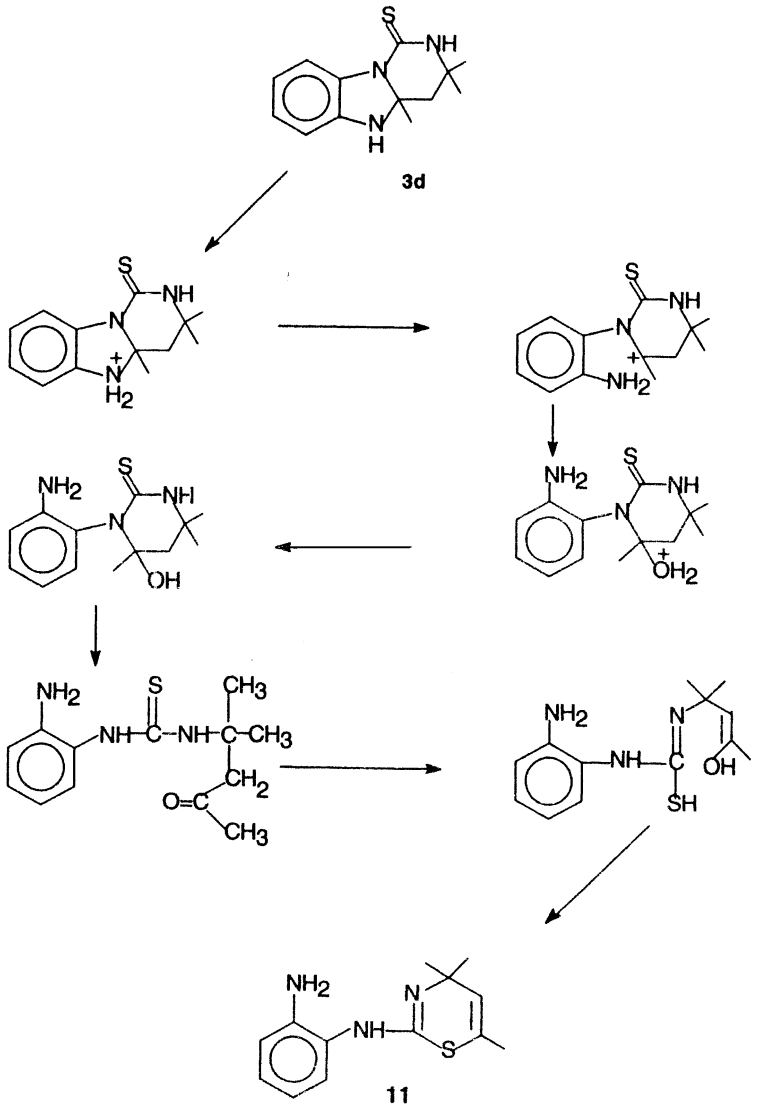


Scheme 2

spectra of **3d** and **3e** [9] show the H_a proton at $\delta = 8.55$ and 8.45 ppm and the NH-proton of imidazole ring at $\delta = 6.50$ and 6.51 ppm. After acetylation the signals of the exchangeable protons disappeared, but a downfield signal for H_a was present at $\delta = 9.20$ and 9.00 ppm confirming that acetylation with an acetic anhydride/acetic acid mixture takes place at the NH-group of the imidazole ring and not at the -C(=S)-NH-moiety of the pyrimidine ring.

Acid catalyzed rearrangement of pyrimidine thione to thiazine has been reported in the literature [18]. Pyrimidobenzimidazoles also undergo similar rearrangement on treatment with acid. Thus, pyrimidobenzimidazole **3d** [9] gave the rearranged product **11** upon heating with 75% H_2SO_4 (Scheme 3). The structure of **11** is supported by correct spectroscopic data. A possible pathway for the formation of **11** from **3d** is outlined in Scheme 3.

Antiinflammatory [19] activity evaluation of **4**, **5**, and **7–11** was performed at 100 mg/kg p.o. Compounds **7** and **8** show 14 and 17% activity, respectively whereas **4**, **5**, **9**, **10**, and **11** were found to be inactive. The pyrimidobenzimidazoles **3b–f** show antiinflammatory [9, 10, 13] activities of 14, 13, 0, 34, and 0% respectively, whereas the corresponding values for **7–11** are 14, 17, 0, 0, and 0%. From this comparison it could be concluded that the conversion of -C(=S)-NH- to -C(=N)-$SCH_2COOC_2H_5$ is of low effect on the antiinflammatory activity, whereas



Scheme 3

conversion of -NH- to -N-$COCH_3$ has an adverse effect. These observations will be helpful in designing new molecules with antiinflammatory properties.

Analgesic activity evaluation [20] of **7** and **8** was carried out at 100 mg/kg p.o. Compounds **7** and **8** show 30 and 20% activity. Recently, pyrimidine derivatives have been reported to be useful in the treatment of cancer [21]; therefore, compounds **4**, **5**, and **7–11** were also secreened for anticancer activity against a small panel of six cancer cell lines consisting of prostate (DU145, PC3), breast (MCF7, MCF7/ADR), melanoma (LOX,SK-MEL-5), colon (HT29), ovarian (IGROV1), and CNS (U251) tumors. GI_{50} (concentration which inhibits the cell growth by 50%) values are summarized in Table 1. The best GI_{50} value was shown by compound **10** against CNS (U251) and was found to be 5.02 μM.

Table 1. Anticancer activity evaluation of compounds **4**, **5**, and **7–11**

	GI_{50} concentration/μM								
	Prostate[a]		Colon[a]	Melanoma[a]		Breast[a]		Ovarian[a]	CNS[a]
	DU145[b]	PC3[b]	HT29[b]	LOX[b]	SK-MEL-5[b]	MCF7[b]	MCF7/ADR[b]	IGROV1[b]	U251[b]
4	> 327.3	–	> 327.4	> 327.4	–	> 327.4	–	> 327.4	35.14
5	368.9	97.2	295.9	290.1	–	–	327.3	–	180.7
7	225.4	73.9	204.5	137.7	–	–	113	–	168.3
8	88.2	19.5	81.8	76.4	–	–	113	–	33.8
9	81.1	87.9	150.7	96.1	–	–	56.6	–	69.4
10	150.99	–	62.58	–	48.07	59.2	–	115.51	5.02
11	88.25	–	68.37	–	105.77	70.52	–	128.62	11.29

[a] Tumor type; [b]cell line

Experimental

Melting points were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FT spectrophotometer. ^{1}H NMR spectra were recorded on Bruker WH-200 and WH-300 spectrometers in a *ca*. 5–15% (w/v) solutions in *DMSO*-d_6 (*TMS* as internal reference). Mass spectra were obtained using an AEI MS-9 double focusing high resolution mass spectrometer at a resolving power of 15000. TLC was performed on silica gel G for TLC (Merck), and spots were visualized by iodine vapour or by irradiation with UV light (254 nm). Column chromatography was performed by using Qualigens silica gel for column chromatography (60–120 mesh).

3,4,4a,5-Tetrahydro-3,3,4a-trimethylpyrimido[1,6-a]naphtho-imidazol-1(2H)-thione (**4**: $C_{17}H_{19}N_3S$)

2,3-Diaminonaphthalene (**1**; 158 mg, 1 mmol) was dissolved in 50 cm^3 MeOH, and 0.2 cm^3 4-isothiocyanato-4-methyl-2-pentanone (1.2 mmole) were added. The *pH* of the reaction mixture was adjusted to ~4 by addition of a drop of H_2SO_4 diluted with MeOH. The reaction contents were heated under reflux for 10 h and the solvent was removed under reduced pressure. The residue was made basic with $NaHCO_3$ solution (10%; 20 cm^3) and stirred at room temperature for 10 min. The reaction contents were filtered, washed with H_2O, and the crude product was crystallized from *THF*/MeOH to give **4**.

Yield: 78%, m.p.: 240°C; IR (KBr): $\nu = 1500$ (Ar), 1610 (C=N), 3200, 3400 (NH) cm^{-1}; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 1.20 (2s, 6H, CH_3+CH_3), 1.45 (s, 3H, CH_3), 2.15 (d, 1H, CH_2), 2.40 (d, 1H, CH_2), 6.80 (s, 1H, Ar), 7.05 (s, 1H, exch, NH), 7.20 (m, 2H, Ar) 7.60 (m, 2H, Ar) 8.65 (s, 1H, exch., C(=S)-NH), 9.10 (s, 1H, Ar) ppm; HRMS (*m/z*): found: 297.12943, calcd. for $C_{17}H_{19}N_3S$: 297.12997.

6-(2,3,6,7,8,8a-hexahydro-7,7,8a-trimethylimidazolo (1,2-c)pyrimidine-5(6H)thioxo)-9β-D-ribofuranosyl purine (**5**; $C_{19}H_{27}N_7O_4S$)

N-Aminoethyl adenosine (**2** [16, 17]; 155 mg, 0.5 mmol) was dissolved in 20 cm^3 MeOH, and 0.1 cm^3 4-isothiocyanato-4-methyl-2-pentanone (0.6 mmol) was added. The reaction contents were stirred at room temperature for 4 days; then the solvent was removed at room temperature. The residue was triturated with petrol ether. The white solid obtained was filtered, washed with petrol ether and then with chilled MeOH, and air dried to give condensed product **5**.

Yield: 92%; m.p.: 150°C; IR (KBr): $\nu = 1490$ (Ar), 1600 (-C=N-), 3200–3500 (OH and NH) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 1.20 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.70 (d+s, 4H, CH_3+1H), 3.55 (m, 2H), 3.75 (m, 2H), 3.95 (q, 1H), 4.15 (m, 2H), 4.40 (t, 1H), 4.60 (m, 2H), 5.15 (d, 1H, exch., OH), 5.25 (q, 1H, exch., OH), 5.50 (d, 1H, OH, exch), 5.95 (d, 1H), 8.30 (s, 1H, Ar), 8.55 (d, 2H, 1H exch., -C(=S)-NH+Ar) ppm; HRMS (*m*/*z*): found: 449.18416 calcd. for $C_{19}H_{27}N_7SO_4$: 449.18451.

Tetrahydro-1-(S-methyl)-3,3,4a-trimethyl-pyrimido [6,1-b]benzthiazole (**6**; $C_{14}H_{18}N_2S_2$)

Pyrimidobenzthiazole **3a** (278 mg, 1 mmol) was dissolved in 100 cm^3 MeOH, and H_2SO_4 was added to adjust the *pH* of the reaction mixture to ~1. The reaction mixture was heated under reflux for 8 h, and then solvent was removed under reduced pressure. The residue was rendered alkaline with $NaHCO_3$ solution. The solid which separated was filtered, washed with H_2O, and air dried. The crude product was recrystallized from $CHCl_3$/petrol ether.

Yield: 57%; m.p.: 90°C; IR (KBr): $\nu = 1587$ (Ar) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 1.25 (2S, 6H, 2×CH_3), 1.65 (s, 3H, CH_3), 2.10 (d, 1H, CH_2), 2.20 (s, 3H, SCH_3), 2.40 (d, 1H, CH_2), 7.10 (m, 2H, Ar), 7.35 (m, 1H, Ar), 7.50 (m, 1H, Ar) ppm; HRMS (*m*/*z*): found: 278.09095, calcd. for $C_{14}H_{18}N_2S_2$: 278.09116.

Ethyl-S-(1-(3,4,4a,5-tetrahydro-3,3,4a,7-tetramethylpyrimido[1,6-a]benzimidazolyl)-thio)-ethanoate (**7**; $C_{18}N_{25}N_3O_2S$)

Pyrimidobenzimidazole **3b** (261 mg, 1 mmol) was dissolved in 50 cm^3 *THF*, and anhydrous K_2CO_3 (180 mg) and 0.25 cm^3 ethyl bromoacetate (1.5 mmol) were added. The reaction contents were heated under reflux for 6 h and then filtered. The solvent from the filtrate was removed under reduced pressure, and the residue was triturated with petrol ether. The solid product was filtered, washed with petrol ether, and air dried. The crude product was crystallized from MeOH to give **7**.

Yield: 65%, m.p.: 150°C; IR (KBr): $\nu = 1490$ (Ar), 1610 (C=N), 1720 ($CH_2COOC_2H_5$), 3200 and 3500 (NH) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 1.10 (t, 3H, CH_2-CH_3), 1.30 (s, 3H, CH_3), 1.60 (d, 6H, CH_3+CH_3), 2.10 (d+s, 4H, CH_3 + 1H of CH_2), 2.65 (d, 1H, CH_2), 4.05 (q, 2H, CH_2-CH_3), 4.30 (d, 1H, SCH_2), 4.50 (d, 1H, SCH_2), 6.6 (d+s, 2H, Ar), 7.10 (s, 1H, exch., NH), 7.60 (d, 1H, Ar) ppm; HRMS (*m*/z) found: 347.16606, calcd. for $C_{18}H_{25}N_3O_2S$: 347.16675.

Ethyl-S-(1-(3,4,4a,5-tetrahydro-3,3,4a-trimethyl-8-nitropyrimido[1,6-a]benzimidazolyl)-thio)-ethanoate (**8**; $C_{17}H_{22}N_4O_4S$)

8 was prepared similarly as described for **7**.

Yield: 66%; m.p.: 155°C (MeOH); IR (KBr): $\nu = 1500$ (Ar), 1600 (C=N), 1750 ($CH_2COOC_2H_5$) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 1.10 (t, 3H, CH_2-CH_3), 1.30 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.20 (d, 1H, CH_2), 2.70 (dd, 1H, CH_2), 4.10 (q, 2H, COOC$H_2$$CH_3$), 4.40 (dd, 2H, SCH_2), 6.8 (d, 1H, Ar), 8.0 (dd, 1H, Ar), 8.50 (d, 1H, Ar), 8.90 (s, 1H, exch., NH) ppm; HRMS (*m*/*z*): found: 378.13584, calcd.: $C_{17}H_{22}N_4O_4S$: 378.13617.

2,3,4,4a-Tetrahydro-3,3,4a-trimethyl-5-acetylpyrimido[1,6-a]benzimidazol-1-thione (**9**; $C_{15}H_{19}N_3OS$)

Pyrimidobenzimidazole **3d** (247 mg, 1 mmol) was added to a mixture of 1.5 cm^3 acetic acid and 1.5 cm^3 acetic anhydride. The reaction mixture was heated under reflux for 2 h and then poured on crushed ice. The white product which separated was filtered, washed with water, and air dried. The crude product was crystallized from *THF*/MeOH to give **9**.

Yield: 41%; m.p.: 205°C; IR (KBr): $\nu = 1493$ (Ar), 1665 (N-$COCH_3$), 3197 (NH) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 1.20 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.20 (d, 1H, CH_2), 2.40 (s, 3H, $COCH_3$), 3.30 (d, 1H, CH_2), 7.0 (m, 2H, Ar), 7.30 (bs, 1H, Ar), 8.80 (s, 1H, exch., SH), 9.20 (d, 1H Ar) ppm; HRMS (*m*/*z*): found: 289.12470, calcd. for $C_{15}H_{19}N_3$ OS: 289.12488

2,3,4,4a-Tetrahydro-3,3-4a-trimethyl-5-acetyl-7-methoxypyrimido[1,6-a]benzimidazol-1-thione (**10**; $C_{16}H_{21}N_3O_2S$)

10 was prepared similarly as described for **9**.

Yield: 30%; m.p.: 185°C (*THF*/MeOH); IR (KBr) $\nu = 1500$ (Ar), 1680 (N-C(=O)-CH_3), 3200 and 3400 (NH) cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 1.20 (2s, 6H, $2\times CH_3$), 1.60 (s, 3H, CH_3), 2.20 (d, 1H, CH_2), 2.40 (s, 3H, $COCH_3$), 3.30 (d, 1H, CH_2), 3.75 (s, 3H, OCH_3), 6.50 (dd, 1H, Ar), 6.90 (bs, 1H, Ar), 8.60 (s, 1H, exch., SH), 9.0 (d, 1H, Ar) ppm; HRMS (*m*/*z*): found: 319.13547, calcd. for $C_{16}H_{21}N_3O_2$ S: 319.13544.

2-(2-Aminoanilino)-4,4,6-trimethyl-1,3-thiazine (**11**; $C_{13}H_{17}N_3S$)

Pyrimidobenzimidazole **3d** (250 mg) and 6 cm^3 75% H_2SO_4 were heated on a water bath for 5 h and then left at room temperature overnight. The reaction mixture was rendered alkaline with NaOH, and the white product separated was filtered, washed with H_2O, and air dried. The crude product was crystallized from *THF*/MeOH to give rearranged product **11**.

Yield: 50%; m.p.: 190°C; IR (KBr): $\nu = 1497$ (Ar), 1597 (C=N), 3445, 3353, 3185 (NH_2 and NH) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 1.20 (s, 6H, $2\times CH_3$), 1.90 (s, 3H, CH_3), 4.50 (s, 2H, exch., NH_2), 5.60 (s, 1H, -CH=C<), 6.50–6.70 (m, 4H, Ar), 7.50 (bs, 1H, exch., =NH) ppm; HRMS (*m*/*z*): found: 247.11441, calcd. for $C_{13}H_{17}N_3S$: 247.11432.

Antiinflammatory activity screening [19]

Antiinflammatory activity testing was carried out using carrageenin-induced paw oedema in albino rats. The oedema in one of the hind paws was induced by injection of 0.1 cm^3 of 1% carrageenin solution 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 group was calculated and compared with the group receiving a standard drug. At 100 mg/kg p.o none of the compounds possessed potent antiinflammatory activity. However, compounds **7** and **8** inhibited the carrageenin induced hind paw oedema by 14 and 17% as compared to the standard drug phenyl butazone which showed 35% activity at 30 mg/kg p.o.

Analgesic activity testing [20]

Analgesic activity was evaluated in albino mice using the phenylquinone writhing assay. Female swiss mice (15–20 g) bred in the Animal House of Central Drug Research Institute, Lucknow, and maintained under standard laboratory conditions, were used in the study. 0.2 cm^3 of 0.02% aqueous solution of phenylquinone (2-phenyl-1,4-benzoquinone) were injected, and the mice were observed for writhing for 20 min. The Number of writhes produced by each mouse was counted during this period. A minimum of 10 writhes produced by a mouse was considered positive and used in the analgesic testing on the following day. The mice consisting of 5 in each group and showing significant writhing were given orally 50 and 100 mg/kg p.o. doses of test compounds 15 min prior to phenyl quinone challenge. Writhing was again recorded for each mouse in a group, and percentage of protection was calculated using the formula *Protection* = 100−(# of writhings for treated mice/#

of writhings for untreated mice)×100. This was taken as the percent analgesic response and was averaged in each group of mice. Percent of animals exhibiting analgesia was determined with each dose. Compounds **7** and **8** were secreened for analgesic activity at 100 mg/kg p.o and exhibited 30 and 20% activity, respectively. Investigations with compounds showing promising activity were repeated and their analgesic activity was thus confirmed.

Anticancer activity screening

Compound **4**, **5**, and **7–11** were tested over a broad concentration range (ten fold dilutions starting from $\geq$100 m*M* to n*M*) against six human cancer cell lines comprised of different tumor types (Table 1) maintained in growing condition in RPMI 1640 medium containing 10% fetal calf serum and incubated at 37°C under a 5% CO_2 atmosphere. All lines were inoculated on a series of standard 96-well microtitre plates on day zero, followed by 24 h incubation in the absence of test compound. The inoculation densities used currently in the screening are as per *Monk et al*. [22]. Compounds **4**, **5**, and **7–11** were dissolved in *DMSO* and diluted further in culture medium. An aliquot of each dilution was added to the growing cells in 96 well plates and incubated for 48 h. After incubation, the assay was terminated by adding 50 cm^3 of trichoroacetic acid and incubating at 4°C for 30 min. The precipitated cells were washed and stained with sulforhodamine B dye for 30 min; the excess dye was washed off with acetic acid. Adsorbed dye was solubilized in *tris* base (alkaline *pH*) and quantitated by measuring the *OD* at 490 min in an ELISA reader. GI_{50} values (concentration which inhibits the cell growth by 50%) were calculated according to *Boyd* and *Pauli* [23] and are summarized in Table 1.

Acknowledgements

We are grateful to the director of CDRI, Lucknow, for providing testing facilities, and to Ms. *U. Sharma* and Mr. *H. C. Verma* for technical help in conducting antiinflammatory and analgesic activity screening respectively. Our sincere thanks go to Prof. *J. W. Lown*, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, Dr. *N. R. Dhamiwal*, Department of Chemistry, Punjabi University of Patiala, and technical staff of the Chemistry Department, University of Roorkee, for spectroscopic studies and microanalyses. Financial help from CSIR, New Delhi (*R. P. Verma*) and from UGC, New Delhi (*N. Singhal*) is greatfully acknowledged.

References

[1] Wolff ME (ed) (1981) Burger's Medicinal Chemistry, part III. Wiley, New York
[2] Cioli V, Putzalu S, Rossi V, Corradino C (1980) Toxicology Appl Pharmacol **54**: 332
[3] Inoue M, Hashimoto K (1992) Jpn Kokai Tokyo Koho Jp 03204, 877 (91, 204, 877); Chem Abstr **116**: 6580z
[4] Goto K (1992) K Jpn Kokai Tokyo Koho Jp 03215488 (91, 215, 488), Chem Abstr **116**: 128962 w
[5] Goto K, Hashimoto K, Kanai K (1989) Jpn Kokai Tokyo Koho Jp. 63, 198, 685 (88, 198, 685); Chem Abstr **110**: 23911b
[6] Shridhar DR, Sastri CVR, Lal KB, Bansal OP, Sondhi SM (1987) Gazette of India, 213; Indian Patent 159118
[7] Shridhar DR, Sastri CVR, Lal KB, Bansal OP, Sondhi SM (1987) Gazette of India, 214; Indian patent 159119
[8] Sondhi SM, Magan A, Mahesh VK, Srimal RC, Goel AK (1994) Indian J Chem **33B**: 1144
[9] Sondhi SM, Magan A, Sahu R, Mahesh VK, Shukla R, Patnaik GK (1994) Synthesis 1175
[10] Sahu R, Magan A, Gupta B, Sondhi SM, Srimal RC, Patnaik GK (1994) Phosph Sulf Silicon **88**: 45

[11] Sondhi SM, Verma RP, Singhal N, Sharma VK, Shukla R, Patnaik GK (1996) Phosph Sulf Silicon **118**: 7
[12] Sondhi SM, Singhal N, Verma RP, Raghubir R, Goel AK, Patnaik GK (1997) Indian J Chem **36B**: 620
[13] Sondhi SM, Sharma VK, Verma RP, Singhal N, Shukla R, Raghubir R, Dubey MP (1999) Synthesis **5**: 878
[14] Sondhi SM, Verma RP, Singhal N, Shukla R, Raghubir R, Dubey MP (1999) Indian Drugs **36**: 50
[15] Mathes RA, Stewart FD, Frank SA Jr (1948) J Am Chem Soc **70**: 1452
[16] Zemlicka J, Owens J (1977) J Org Chem **42**: 517
[17] Sondhi SM, Xie J, Modak AS, Bashkin JK (1998) Indian J Chem Sec B **37B**: 1097
[18] Singh H, Singh P (1980) J Chem Soc Perkin I, 1013
[19] Winter CA, Risley EA, Nuss GW (1962) Proc Soc Exp Biol Med **111**: 544
[20] Singh PP, Junnarkar AY, Seshagiri Rao C, Varma RK, Shridhar DR (1983) Meth Find Exptl Clin Pharmacol **5**: 601
[21] Blankley CJ, Boschelli DH, Doherty AM, Hamby JM, Kluetchko S, Panek RL (1998) US 5, 733, 914; Chem Abstr **128**: 257440w
[22] Monks A, Scudiero D, Skehan P, Shoemaker R, Paull K (1991) J Natl Cancer Inst **83**: 757
[23] Boyd MR, Pauli KD (1995) Drug Dev Res **34**: 91

Received October 29, 1999. Accepted (revised) January 13, 2000