Monatshefte für Chemie 131, 511–520 (2000)

Monatshefte für Chemie
Chemical Monthly

Synthesis and Anticancer, Antiinflammatory, and Analgesic Activity Evaluation of Some Sulfa Drug and Acridine Derivatives

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Summary. Various sulfa drugs were condensed with 4-isothiocyanato-4-methyl-2-pentanone at *pH*∼3–5 by refluxing in methanol to give various substituted mercaptopyrimidines. On condensation with 9-chloro-2-substituted or -unsubstituted acridines, sulfathiazole gave the corresponding condensed products. N-Ethylaminoadenosine reacted with 9-chloroacridine to the coupled product. Condensation of sulfathiazole with 9-isothiocyanato-2,4-substituted or -unsubstituted acridines afforded the corresponding condensed compounds. The structures of all synthesized compounds were confirmed by spectroscopic methods. Anticancer, antiinflammatory, and analgesic activities of all compounds were investigated.

Keywords. Sulfa drug; Acridine derivatives; Anticancer; Antiinflammatory; Analgesic.

Introduction

Cancer and inflammatory diseases continue to be a major problem for mankind. Many inflammation inhibitors such as phenylbutazone, oxyphenbutazone, ibuprofen, indomethacin, dichlofenac, ketoprofen, *etc*. are available, but these drugs have the serious side effects of ulcerogenic activity [1] and hence cannot be used permanently. Only few anticancer drugs are available, stimulating the development of new and safer antiinflammatory remedies [2–4] and the search for new anticancer agents [5–7]. Pyrimidine and acridine derivatives possessing antitumor [7–9], antiinflammatory [10–12], and analgesic [13] activities have been reported in the literature. In continuation of our efforts in search of potential antiinflammatory [14–23] and anticancer agents [24] we have synthesized pyrimidine derivatives of sulfa drugs and a variety of derivatives of acridines and screened them for antitumor, antiinflammatory, and analgesic activities.

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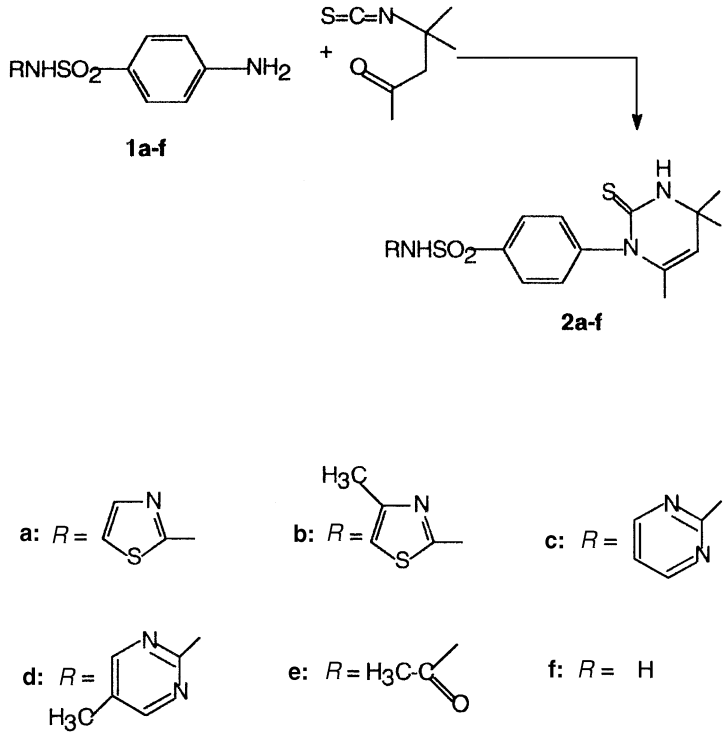


Scheme 1

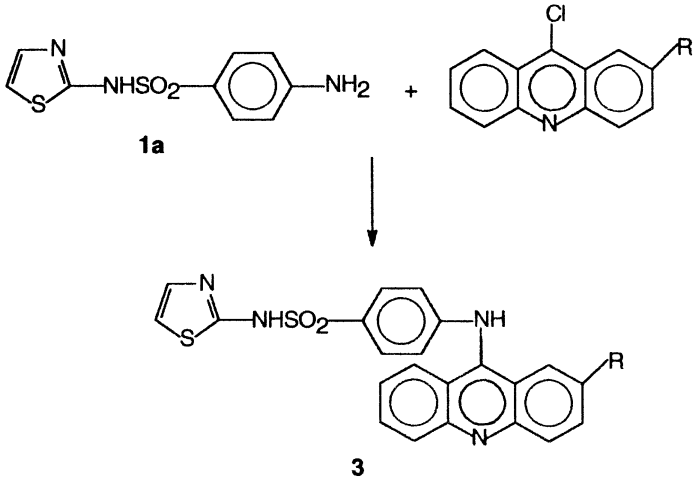
Results and Discussions

Condensation of sulfathiazole **1a** (Scheme 1) with 4-methyl-4-isothiocyanato-2-pentanone gave **2a** in good yield. The spectroscopic properties of **2a** were found to be in accordance with its structure. Similarly, compounds **2b–f** (Scheme 1) were synthesized. The physical constants and spectroscopic data of **2a–f** fully support the assigned structures.

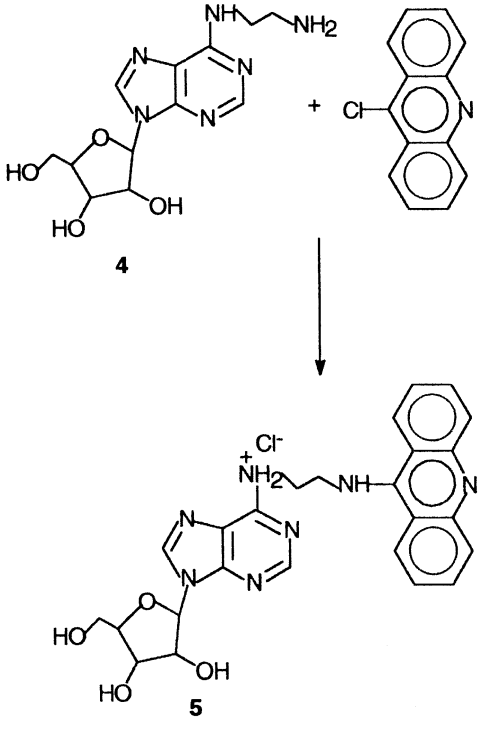
Sulfathiazole **1a** (Scheme 2) and 9-chloro-2-methyl-acridine [25, 26] were dissolved separetely in methanol; after mixing at room temperature they were allowed to stand for two days. The product **3a** displayed the corresponding spectroscopic data. Similarly, compound **3b** was synthesized.

N-Ethylaminoadenosine was synthesized according to Ref [27]. Condensation of N-ethylaminoadenosine (**4**) with 9-chloroacridine was carried out at room temperature to give compound **5** (Scheme 3). Physical constants and spectroscopic data of **5** were found to be in full agreement with its structure.

9-Isothiocyanatoacridine (**6a**) 9-isothiocyanato-2-methylacridine (**6b**), and 9-isothiocyanato-4-methylacridine (**6c**) were synthesized by the method reported in Ref. [28]. Condensation of sulfathiazole with **6a** was carried out at room temperature using *THF* as solvent to yield **7a** (Scheme 4). Similarly, sulfathiazole **1a** was condensed with 9-isothiocyanato-2-methylacridine (**6b**) and 9-isothiocyanato-4-methylacridine (**6c**) to afford the corresponding products **7b** and **7c**. The structures of compounds **7** were confirmed by their physical and spectroscopic properties.



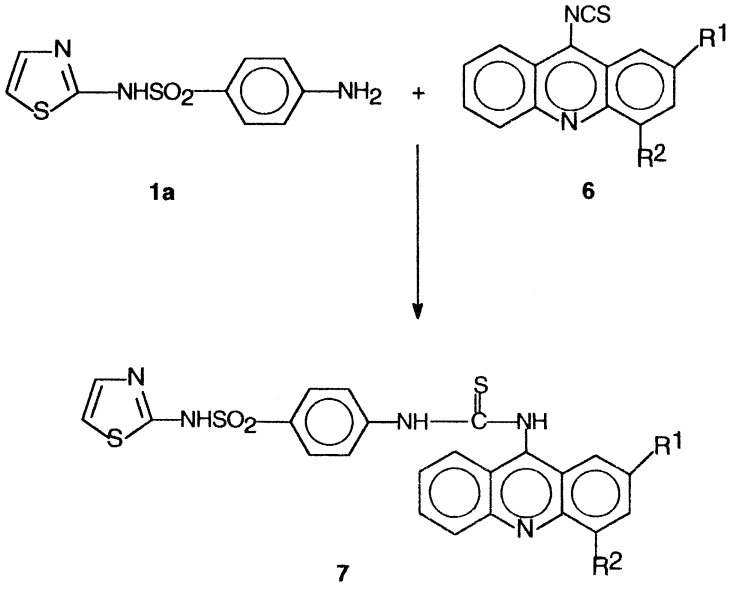
Scheme 2



Scheme 3

Anticancer activity evaluation

Anticancer activity evaluation [29, 30] of **2a–f**, **3a**, **b**, **5**, and **7c** was carried out against a small panel of six cancer cell lines consisting of prostate (DU145) colon (HT29) melanoma (LOX), breast (MCF, MCF7/ADR), CNS (U251), and ovarian



a: $R^1 = R^2 = H$; **b:** $R^1 = CH_3$, $R^2 = H$; **c:** $R^1 = H$, $R^2 = CH_3$

Scheme 4

Table 1. Antitumor activity evaluation of compounds **2a–f**, **3a**,**b**, **5**, and **7c**

GI_{50} Concentration/μ*M*							
	Prostate[a]	Colon[a]	Melanoma[a]	Breast[a]	Breast Resistant[a]	CNS[a]	Ovarian[a]
	DU 145[b]	HT 29[b]	LOX[b]	MCF[b]	MCF 7/ADR[b]	U251[b]	OVCAR3[b]
2a	237.8	193.9	132.3	–	292.8	141.8	–
2b	>552.7	516.95	42.48	>552.7	>552.7	>552.7	–
2c	132.9	111.2	90.5	132.7	>335.7	94.5	–
2d	75	82.4	70.3	95.7	129.9	153.3	–
2e	63	60.5	57.7	40	76.2	83.2	–
2f	76.21	66.29	94.13	209	81.89	147.32	–
3a	94.4	37.65	44.9	61.23	78.68	69.98	–
3b	28.7	16.4	–	20.8	>570.1	44.4	22.1
5	8.59	8.16	5.55	7.72	5.06	9.41	–
7c	>263.9	6.7	–	77.8	36.6	>263.9	66.7
Doxo	0.1	0.5	0.02	0.26	2.2	0.1	–

[a] Tumor type; [b]cell line

(OVCAR 3) tumors. The effect of the compounds screened is expressed in terms of 50% growth inhibiting concentration (GI_{50}). The GI_{50} values (μM concentration) of **2a–f**, **3a**, **b**, **5**, and **7c** are reported in Table 1. From Table 1 it can be seen that best GI_{50} values are shown by **5** (8.59 μM, prostate tumor, cell line DU145), **7c** (6.7 μM, colon tumor, cell line HT29), **5** (5.55 μM, melanoma tumor, cell line LOX), **5** (7.72 μM, breast tumor, cell line MCF), **5** (5.06 μM, breast tumor, cell line MCF7/ADR), **5** (9.41 μM, CNS tumor, cell line U251), and **3b** (22.1 μM, ovarian tumor, cell line OVCAR 3). From the GI_{50} values of **2a–f**, **3a**, **b**, **5**, and **7c** it is clear that acridine derivative **5** gave good results against prostate, melanoma, breast, breast resistant, and CNS tumors, and acridine derivatives **3b** and **7c** gave good results against ovarian and colon tumors.

Antiinflammatory and analgesic activity screening

Antiinflammatory activity evaluation [31] of compounds **2a–f**, **3a**, **b**, **5**, and **7b**, **c** was carried out at 100 mg/kg p.o. in rats using carrageenin induced paw oedema. Compounds **2b**, **3b**, and **5** showed 7,8.5, and 25.5% activity, respectively, whereas others showed no effect. Analgesic activity [32] of compounds **2a–f**, **3a**, **b**, and **7b**, **c** was evaluated by the writhing assay. Compounds **2b**,**c**,**e**,**f**,**3a**,**b** and **7b**,**c** exhibited 50, 25, 25, 25, 20, 50, 50 and 25% analgesic activity at 100 mg/kg p.o.; compounds **2b**,**c**,**3a**,**b**, and **7b** displayed 25, 25, 20, 25, and 25% activity at 50 mg/kg p.o. Compounds **2a** and **2b** were found to be inactive.

Experimental

Melting points were determined on a JSGW apparatus and are uncorrect. IR spectra were recorded using a Perkin Elmer 1600 FT spectrophotometer. ^{1}H NMR spectra were measured on a Bruker WH-300 spectrometer in *ca*. 5–15% (w/v) solution in *DMSO*-d_6 (*TMS* as internal standard). The mass spectra were obtained with a double focusing high resolution mass spectrometer at a resolving power 15000. TLC was performed on silica gel G for TLC (Merek), 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).

Reaction of **1** *with 4-methyl-4-isothiocyanato-2-pentanone; general procedure*

Sulfathiazole **1a** (225 mg, 1 mmol) was dissolved in 50 cm^3 MeOH, and 0.16 cm^3 (1 mmol) 4-methyl-4-isothiocyanato-2-pentanone were added. A few drops of a 10% solution of H_2SO_4 in MeOH was added to adjust the *pH* of the reaction mixture to 4–5. After about 1 h of refluxing a white solid started to separate. After further 7 h of refluxing, the reaction was allowed to stand overnight. The solid product was filtered, washed thoroughly with MeOH, $NaHCO_3$ solution, H_2O, and MeOH, and air dried to give pure **2a**.

4-(1,2,3,4-Tetrahydro-4,4,6-trimethyl-2-thioxo-1-pyrimidinyl)-N-(2-thiazolyl)-bezene sulfonamide (**2a**; $C_{16}H_{18}N_4O_2S_3$)

Yield: 235 mg (59%); m.p.: 210–213°C; IR (KBr): $\nu = 3433$ (NH), 1693 (C=N), 1570, 1532 (Ar), 1338, 1145 ($NHSO_2$) cm^{-1}; ^{1}H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 1.3 (3s, 9H, 3×CH_3), 5.0 (s, 1H C=CH), 6.85 (d, 1H, Ar), 7.10 (d, 1H, Ar), 7.30 (m, 2H, Ar), 7.80 (m, 2H, Ar) ppm; HRMS (*m*/*z*): found: 394.05711, calcd. for $C_{16}H_{18}N_4O_2S_3$: 394.05920.

4-(1,2,3,4-Tetrahydro-4,4,6-trimethyl-2-thioxo-1-pyrimidinyl)-N-(4-methyl-2-thiazolyl)-benzene sulfonamide (**2b**; $C_{17}H_{20}N_4O_2S_3$)

Yield: 66%; m.p.: 208°C; IR (KBr): $\nu = 3429$ (NH), 1694 (C=N), 1640, 1548 (Ar), 1321, 1155 ($NHSO_2$) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 1.40 (3s, 9H, $3 \times CH_3$), 2.45 (s, 3H, CH_3), 5.0 (s, 1H, C=CH), 7.30 (dd, 2H, Ar), 7.70 (dd, 2H, Ar) ppm; MS: *m/z* (rel. int.) = 408 (M^+, 38), 393 (M^+-CH_3, 98), 350 (M^+-SCN, 9), 349 (M^+-HSCN, 18), 334 (M^+-(CH_3+HSCN), 15), 295 (5), 268 (7), 251 (4), 236 (5), 231 (9), 215 (39), 177 (10), 172 (18).

4-(1,2,3,4-Tetrahydro-4,4,6-trimethyl-2-thioxo-1-pyrimidinyl)-N-(2-pyrimidinyl)-benzene sulfonamide (**2c**; $C_{17}H_{19}N_5O_2S_2$)

Yield: 63%; m.p.: 225°C; IR (KBr): $\nu = 3367$ (NH), 1446 (Ar), 1367, 1161 ($NHSO_2$) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 1.40 (3s, 9H, $3 \times CH_3$), 5.0 (s, 1H, C=CH), 7.0 (t, 1H, Ar), 7.31 (d, 2H, Ar), 7.95 (dd, 2H, Ar), 8.39 (d, 2H, Ar) ppm; MS: *m/z* (rel. int) = 339 (M^+, 100), 330 (M^+-HSCN, 6), 251 (5), 249(3), 231 (21), 215 (66), 172 (13), 158 (13), 156(6).

4-(1,2,3,4-Tetrahydro-4,4,6-trimethyl-2-thioxo-1-pyrimidinyl)-N-(5-methyl-2-pyrimidinyl)-benzene sulfonamide (**2d**; $C_{18}H_{21}N_5O_2S_2$)

Yield: 92% m.p.: 230°C; IR (KBr): $\nu = 3431$ (NH), 1637 (C = N), 1456 (Ar), 1373, 1159 ($NHSO_2$) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 1.4 (3s, 9H, $3 \times CH_3$), 2.23 (s, 3H, CH_3), 5.0 (s, 1H, C=CH), 6.75 (d, 1H, Ar), 7.30 (dd, 2H, Ar), 7.90 (dd, 2H, Ar), 8.20 (d, 1H, Ar) ppm; MS: *m/z* (rel. int.) = 403 (M^+, 48), 388 (M^+-CH_3, 100), 345 (M^+-SCN, 4), 344 (M^+-HSCN, 6), 329 (M^+-(CH_3 +HSCN, 6), 263 (4), 231 (20), 215 (64), 172 (11), 155 (3).

4-(1,2,3,4-Tetrahydro-4,4,6-trimethyl-2-thixo-1-pyrimidinyl)-N-acetyl-benzene sulfonamide (**2e**; $C_{15}H_{19}N_3O_3S_2$)

Yield: 97%; m.p.: 178°C (MeOH); IR (KBr): $\nu = 3365$ (NH), 1717 (C(=O)-NH), 1453 (Ar), 1368, 1163 ($NHSO_2$) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 1.40 (3s, 9H, $3 \times CH_3$) 5.0 (s, 1H, C=CH), 7.40 (dd, 2H, Ar), 7.90 (dd, 2H, Ar) ppm.

4-(1,2,3,4-Tetrahydro-4,4,6-trimethyl-2-thioxo-1-pyrimidinyl)-benzene sulfonamide (**2f**; $C_{13}H_{17}N_3O_2S_2$)

Yield: 95%; m.p.: 191°C (MeOH); IR (KBr): $\nu = 3391$ (NH), 1640 (C=N), 1592, 1538 (Ar), 1333, 1161 ($NHSO_2$) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 1.40 (3s, 9H, $3 \times CH_3$) 5.04 (s, 1H, C=H), 7.40 (dd, 2H, Ar), 7.90 (dd, 2H, Ar) ppm.

4-(2-Methyl-9-aminoacridinyl)-N-(2-thiazolyl)-benzene sulfonamide (**3a**; $C_{23}H_{18}N_4O_2S_2$)

Sulphathiazole **1a** (255 mg, 1 mmol) and 9-chloro-2-methylacridine (240 mg, 1 mmol) were dissolved separately in methanol (20 cm^3 for each) by warming. These solutions were cooled to room temperature and mixed. The reaction mixture was allowed to stand at room temperature for two days. The yellow solid that separated was filtered, washed with methanol, and air dried to give **3a**. Work-up of the mother liquor did not give any additional product.

Yield: 210 mg (51%); m.p.: 270°C; IR (KRr): $\nu = 3493$ (NH), 1522 (Ar), 1308, 1150 ($NHSO_2$) cm^{-1}, ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 2.25 (s, 3H, CH_3), 6.8 (d, 1H, Ar), 7.25 (d, 1H, Ar), 7.45 (m, 3H, Ar), 8.0 (m, 8H, Ar) ppm; MS: (*m/z* (rel. int.) = 446 (M^+, 0.2), 239 (2) 208 (100), 207 (6).

4-(9-Aminoacridinyl)-N-(2-thiazolyl)-benzene sulfonamide (**3b**; C_{22} $H_{18}N_4O_2S_2$)

3b was prepared similarly as described for **3a**. Yield: 87%; m.p.: 268°C; IR (KBr): $\nu = 3390$ (NH), 1631 (C=N), 1569, 1512 (Ar) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 6.8 (d, 1H, Ar), 7.15 (d, 1H, Ar), 7.45 (m, 4H, Ar), 7.85 (dd, 2H, Ar), 7.95 (m, 4H, Ar), 8.10 (d, 2H, Ar) ppm.

N-(2-Ethylamino-9-acridinyl)-adenosine hydrochloride (**5**; $C_{25}H_{26}N_7O_4Cl$)

N-Ethylaminoadenosine (**4**; 155 mg, 0.5 mmol) and 9-chloroacridine (107 mg, 0.5 mmol) were dissolved in 40 cm^3 methanol and allowed to stand at room temperature for 3 days. Then solvent was allowed to evaporate at room temperature to dryness. The solid residue was washed thoroughly with diethyl ether and then crystallized from methanol to give pure **5**.

Yield: 135 mg (55%); m.p.: 162°C; IR (KBr): $\nu = 3429$ (NH, OH), 1628 (C=N), 1467 (Ar) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 3.60 (m, 2H), 4.0 (m, 2H), 4.15 (m, 1H), 4.25 (m, 1H), 4.60 (m, 1H), 5.5 (m, 2H), 5.90 (d, 1H), 7.5 (m, 2H, Ar), 8.0 (m, 4H, Ar), 8.30 (m, 3H, Ar), 8.70 (d, 1H, Ar) ppm; MS: *m/*z (rel.int). = 194 (100), 193 (88), 178 (53), 160 (31).

Reaction of **1** *with 9-isothiocyanatoaridine; general procedure*

Sulfathiazole **1a** (510 mg, 2 mmol) and 9-isothiocyanatoacridine (472 mg, 2 mmol) were dissolved separately in 50 cm^3 and 150 cm^3 *THF*, respectively, by warming. Then both solutions were cooled to room temperature and mixed. The mixture was stirred at room temperature for 2 days, and the solvent was allowed to evaporate at room temperature. The solid residue was dissolved in a minimum amount of *THF* together with a few drops of *DMF* and was adsorbed on silica gel. Column chromatography on silica gel and elution with CCl_4:ethyl acetate (2:8) first gave some side products and then condensed product **7a**.

N-(9-Acridinyl)-N′-(4(N-(2-thiazolyl)-benzene sulfonamido)-thiourea (**7a**; $C_{23}H_{17}N_5O_2S_3$)

Yield: 5%; m.p.: 162°C (CCl_4: ethyl acetate (2:8)); IR (KBr): $\nu = 3371$ (NH), 1578, 1470 (Ar) cm^{-1}; ^1H NMR (300 MHz, δ,*DMSO*-d_6): 6.80 (d, 1H, Ar), 7.30 (m, 3H, Ar), 7.60 (m, 5H, Ar), 7.75 (m, 2H, Ar), 7.85 (t, 1H, Ar), 8.2 (d, 2H, Ar), 10.95 (s, 1H, NH, exch.), 12.5 (bd, 2H, 2 × NH, exch.) ppm; MS: *m/*z (rel. int.) = 373 (3), 194 (16), 193 (3), 178 (5), 163 (5).

N-(2-Methyl-9-acridinyl)-N′-(4-N-(2-thiazolyl)-benzene sulfonamido)-thiourea (**7b**; $C_{24}H_{19}N_5O_2S_3$)

Yield: 38%; m.p.: 215°C (CCl_4: ethyl acetate (2:8)); IR (KBr): $\nu = 3469$ (NH) cm^{-1}; ^1H NMR (300 MHz, δ,*DMSO*-d_6): 2.3 (s, 3H, CH_3), 6.70 (t, 2H, Ar), 7.10 (bs+t, 3H, 1H, NH+2H, Ar), 7.50 (bs+m, 9H, 2H, 2 × NH,+7H, Ar), 7.90 (s, 1H, Ar), 8.15 (d, 1H, Ar) ppm; MS: *m/z* (rel. int.) = 208 (6), 207 (6), 192 (4), 163 (3).

N-(4-Methyl-9-acridinyl)-N′-(4-N-(2-thiazolyl)-benzenes sulfonamido))-thiourea
(**7c**; $C_{24}H_{19}N_5O_2S_3$)

Yield: 33%; m.p.: 195–200°C (CCl_4: ethyl acetate (2:8)); IR (KBr): $\nu = 3450$ (NH), 1494 (Ar), 1311, 1139 ($NHSO_2$) cm^{-1}l ^1H NMR (300 MHz, δ, *DMSO*-d_6+D_2O): 2.7 (s, 3H, CH_3), 6.65 (m, 3H, Ar), 7.10 (d, 1H, Ar), 7.50 (m, 3H, Ar), 7.80 (d, 1H, Ar), 7.95 (m, 1H, Ar), 8.15 (m, 2H, Ar), 8.35 (d, 1H, Ar), 8.50 (d, 1H, Ar) ppm; MS: *m/z* (rel. int.) = 297 (5), 251 (26) 250 (8), 235 (8),208 (76), 207 (22).

Anticancer activity screening

Compounds **2a–f**, **3a**,**b**,**5**, and **7a–c** were tested over a broad concentration range (ten fold dilutions starting from $\geq$100 m*M* to 10 n*M*) against six human cancer cells lines comprised of different tumor types and maintained in growing conditions in RPMI 1640 medium containing 10% fetal calf serum and incubated at 37°C under 5% CO_2 atmosphere. All cells lines were inoculated on a series of standard 36 well microtitre plates on day zero, followed by 24 h incubation in the absence of test compound. The inoculation density used currently in the screening are as per *Monk et al.* [29]. All test compounds 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 trichloroacetic acid and incubating at 4°C for 30 min. The precipitated cells were washed and stained with sulforhodamine B dye for 30 min, and 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 nm in an ELISA reader. GI_{50} values were calculated according to *Boyd* and *Pauli* [30] and are reported in Table 1.

Antiinflammatory activity screening

Antiinflammatory activity screening [31] was carried out using carrageenin-induced paw oedema in albino rats obtained from the animal facility of the Central Drug Research Institute, Lucknow, and maintained under standard laboratory conditions. The oedma in one of the hind paws was induced by injection of carrageenin (100 mm^3 of 1%) into planter aponeurosis. The volume of the paw was measured plethysmographically immediately after and three hours after the injection of the irritant. The difference in volume gave the amount of oedema developed. Percent inhibition of the oedema between the control group and compound treated groups was calculated and compared with the group receiving a standard drug. At 100 mg/kg p.o, compounds **2b**, **3b** and 5 inhibited the carrageenin induced hind paw oedema by 7, 8.5, and 25.5%, respectively, as compared to the standard durg phenylbutazone which showed 35% activity at 30 mg/kg p.o.

Analgesic activity evaluation

Analgesia was measured by the writhing assay [32] using Swiss mice (15–20 gm) bred in the Animal House of the Central Drug Research Institute, Lucknow, and maintained under standard laboratory conditions. Female mice were screened for writhing on day 1 by injecting intraperitoneally 0.2 cm^3 of a 0.02% aqueous solution of phenylquinone. They were kept on a flat surface, and the number of writhes of each mouse was recorded for 20 minutes. The mice showing significant (> 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 50 or 100 mg/kg p.o. dose of the test compounds 15 min prior to phenyl quinone challenge. Writhing was again recorded for each mouse in a group, and a percentage protection was calculated using formula. $Protection = 100 - [(\#\text{ of writhings for treated mice}/\#\text{ of writhings for untreated mice}) \times 100$. 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. Compounds **2a–f**, **3a**,**b**,**5**, and **7b**,**c** were screened for analgesic activity. Compounds **2b**,**c**,**e**,**f**, **3a**,**b**, and **7b**,**c** showed 50, 25, 25, 25, 20, 50, 50, and 25% protection at 100 mg/kg p.o.; compounds **2b**,**c**, **3a**,**b**, and **7b** showed 25, 25, 20, 25, and 25% activity at 50 mg/kg p.o., respectively. Compounds **2a** and **2d** did not elicit significant analgesic activity.

Acknowledgements

We are grateful to the head of CDRI, Lucknow, Prof. *J. W. Lown*, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, and the technical staff of the Chemistry Department,

University of Roorkee, for spectroscopic studies. Our sincere thanks go 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 tests, respectively. Financial help from UGC, New Delhi (N. Singhal) is gratefully acknowledged.

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Received November 18, 1999. Accepted (revised) January 12, 2000